UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA,	)	
	)	
Plaintiff,	)	
	)	
v.	)	**Civil Action No. 99-CV-2496 (GK)**
	)	
PHILIP MORRIS USA INC. (f/k/a PHILIP MORRIS INCORPORATED), et al.,	)	**Next Court Appearance: Trial (ongoing)**
	)	
Defendants.	)	

WRITTEN DIRECT EXAMINATION OF DR. MICHAEL DIXON SUBMITTED BY THE JOINT DEFENDANTS PURSUANT TO ORDER #471

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Q: Please state your full name and current title.

A: I am Dr. Michael Dixon, and I am a Senior Scientific Advisor to British American Tobacco (Investments) Limited.

Q: Is that company also known as "BATCo"?

A: Historically it was, because its previous name was the British American Tobacco Company Limited. Some people still call it "BATCo" today.

Q: Where is BATCo based?

A: The head office is in London, England.

Q: And you are English?

A: Yes, I was born in Nottingham in the middle of England.

Q: Do you understand that you are testifying as an expert witness in this case?

A: I do.

Q: Are you receiving any compensation from BATCo, or from any other source, for your testimony in this case.

A: No. I receive compensation as an employee of BATCo, but it is not related to my giving testimony.

Q: How long have you held your current position with BATCo?

A: Since March 2000.

Q: And did you hold any positions with BATCo prior to 2000?

A: Yes, formerly, I managed a group dealing with sensory and behavioral research relating to cigarettes and cigarette smoking at the BATCo R&D Centre in Southampton, England.

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Q: What is the area of expertise for which your testimony is being offered in this case?

A; I am a scientist, in particular a physiologist, with expertise in sensory, behavioral and physiological responses to smoking, and the smoker's responses to specific components of tobacco smoke, such as nicotine. I also have expertise in the design of cigarettes, and the relationship between design parameters and smoker responses. I understand that I will be asked to opine on factors which determine smoking behavior, and in particular the role of nicotine in the sensory response to smoking.

Q: Could you please tell the court about your educational qualifications, in so far as they relate to your expertise?

A: Yes. I graduated from Loughborough University of Technology in 1972 and obtained a B.Sc degree in Human Biology. The main elements of my B.Sc course comprised of human physiology and anatomy, biochemistry, experimental design and statistical methods. This was followed by a three year Research Studentship (sponsored by the U.K. Science Research Council) at London University (St. George's Medical School - Department of Physiology). In 1975, I received a Ph.D. in respiratory physiology following the completion and submission of my thesis entitled "The Effects of the Inhalation of Irritant Gases on the Reflex Control of Breathing in the Rabbit." After receiving my Ph.D., I did a one-year Post Doctoral Research Fellowship at Nottingham University in aspects of work physiology on production line workers in the automobile industry. From 1977 to date the majority of my work has been as a scientist within the pharmaceutical and tobacco industries.

Q: And have you published any scientific papers on subjects relevant to your expert testimony?

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A: Yes, I have published fourteen papers which are directly concerned with smoking behavior, as well as nearly thirty papers on various aspects of respiratory physiology which are not specifically about smoking.

Q: For how long have you been involved professionally in evaluating the determinants of smoking behavior?

A: I have worked in the area of smoking behavior for more than twenty years, both for tobacco companies and for an institution called the Midhurst Medical Research Institute.

Q: Can you give the Court some specific examples of relevant research you have conducted?

A: Certainly. I have done a great deal of research to determine the uptake and absorption of tobacco smoke constituents, in the mouth, the upper respiratory tract, and the respiratory system in general. I have looked at the behavioral aspects of smoking, and how these affect uptake and absorption of constituents. I have examined the relationship between sensory responses to tobacco smoke and the site and quantity of smoke uptake. I have helped develop techniques and data analysis methods for the evaluation of tobacco products, both by expert panels and by consumers. I have looked at ways of incorporating this understanding of smoker responses into product design, and especially into the development of acceptable reduced delivery - or "low tar" - cigarettes. I have studied the historical development of the science of smoking behavior, including our historical understanding of the role of nicotine in smoking. Very recently I was invited to represent CORESTA on a working party formed by the World Health Organization and the International Standards Organisation (ISO) to critically review the ISO smoking machine standard and, if necessary, make recommendations for changes or improvements. The first meeting of the working party will take place in April, 2005.

Q: Dr Dixon, have you appeared as an expert witness prior to the current case?

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A: Yes, I have given depositions or testified at trial for BATCo and its sister company in the United States, Brown and Williamson, on a number of occasions.

Q: Did you receive any compensation for any of this testimony?

A: No. I have received no additional compensation, beyond my regular salary and benefits as an employee of BATCo, for appearing as an expert witness.

Q: Dr. Dixon, what is smoking behavior?

A: Smoking behavior is how the smoker interacts with the cigarette. It generally consists of three things: first, the mechanics of smoking or how a smoker puffs on his or her cigarette; second, the sensory responses that the smoke provides to the smoker; and, third, how the mechanics and sensory responses relate to the design of a cigarette and how the design of a cigarette can affect the yield and consumer acceptability of a cigarette.

Q: Let's start with smoking mechanics. What are smoking mechanics?

A: Smoking mechanics are basically how the person physically smokes the cigarette. Most people don't realize that the act of smoking is in fact a two step process. First is the puff, which is entirely a mouth process, and the second is the inhalation which occurs after the puff is done.

Q: So there are two separate and distinct actions involved in taking smoke into the lungs?

A: Yes.

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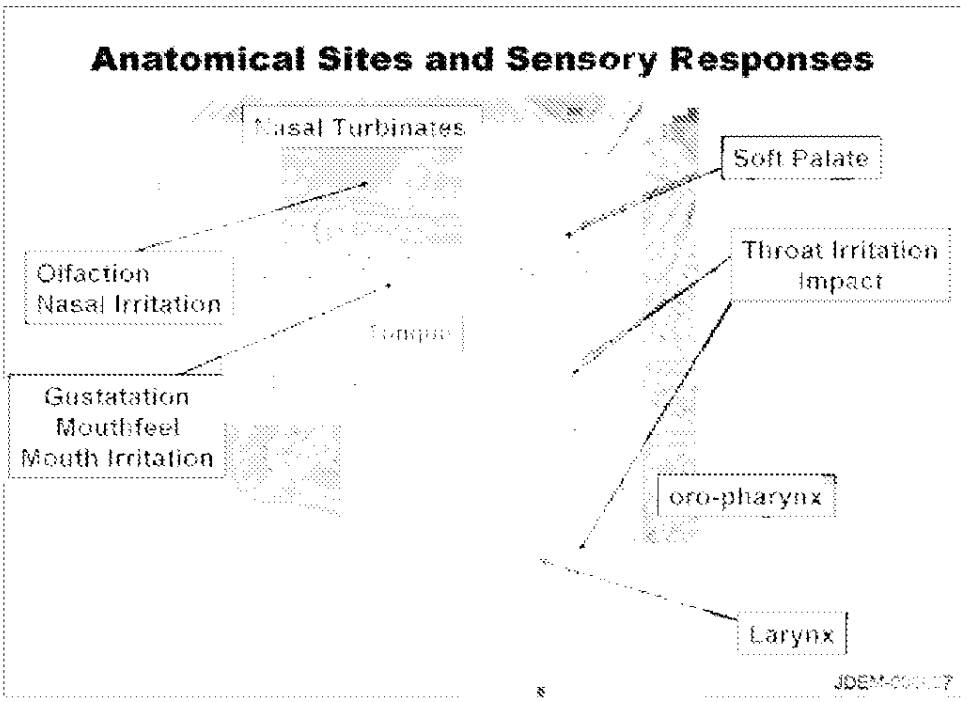

Q: Now, could you explain the first step – the puff -- using JDEM-030007.

A: Yes. This demonstrative is a schematic of a person's head which shows the mouth and the upper airway. The soft palate is a muscular flap which sits in the back of the mouth. The purpose of that soft palate is to contract and form a seal by closing off the mouth from the throat and the rest of the airway. With the soft palate closed one can create a negative pressure in the mouth, and this enables people to suck on things like cigarettes and drinking straws. When a person smokes, the cigarette is obviously placed between the lips, and just before the puff starts, the soft palate contracts and seals the mouth from the rest of the airway; the tongue depresses slightly and that creates a vacuum inside the mouth. That vacuum causes smoke to come from the cigarette through the filter and into the mouth. The mouth is the only place to which the smoke can gain access during the puff. During the puff the smoke does not have access to the rest of the respiratory system.

Q: What is the second step?

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A: Most cigarette smokers, not all, then inhale the smoke. Shortly after the end of the puff, the soft palate relaxes and reverts back to its mid position. This removes the seal between the mouth and throat. The mouth opens, and the smoker inhales ambient air. As that air is drawn into the mouth, it sweeps the smoke past the soft palate and into the throat area or, in physiological terms, the pharyngeal region. The smoke continues past the pharyngeal region into the larynx through the trachea and down into the lung. That is called the inhalation process.

Q: Turning to the sensory responses, what are the sensory responses that a smoker gets from smoking a cigarette?

A: As described in JDEM-030008, there are basically three main classes of sensory responses which are involved when a person smokes a cigarette. The first is called taste or gustation. As with any food or drink, smoke taste is sensed on taste buds on the tongue and the roof of the mouth. As defined physiologically the term taste or gustation is restricted to the sensations of sweet, sour, salty and bitter. As defined, taste or gustation plays only a minor role in cigarette smoking.

Q: What is the second major class?

A: The second major class of sensory response is called olfaction. In common terms, it is called smell or aroma. And that is sensed in the nasal region and it's a very important sensation for distinguishing between different products during drinking, eating, and smoking. Physiologically, olfaction is complex and involves many more dimensions than the four basic taste dimensions. For example in terms of true taste, an apple and a pear are very similar as they both taste sweet. However, people clearly discriminate between an apple and a pear, and this is done through the sense of olfaction rather than physiological taste or gustation. Foods, drinks and tobacco smoke contain volatile flavor compounds. These are released when the substances are placed in the mouth and then the compounds migrate past the soft palate through the throat region and then into the olfactory area of the nose where they give rise to a whole range of sensations. Differences in olfactory sensations enable smokers to distinguish between different styles of cigarettes, for

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example between a U.S. blended cigarette and a UK flue-cured cigarette. A combination of the olfactory and gustatory responses to a substance is defined as the flavor of the substance.

Q: And what is the third major class of sensory responses?

A: The third one is called the common chemical sense. This was a term that was adopted many years ago and is used to describe general sensory responses which are not produced by the specialized receptors involved in gustation or olfaction. It's the result of the stimulation of unspecialized nerve endings which are present in the mouth, the nose and the upper airway. The key common chemical sense responses to cigarette smoke are mouthfeel or mouthful, warmth or coolness, irritation and a response that is referred to as impact, hit or throat catch.

Q: Could you further describe the irritation response?

A: The irritation response is a tingling, peppery sensation like one would experience from eating a chili pepper. The intensity of the response builds gradually. Mouth and throat irritation occur during smoking, but obviously to a lesser extent than the irritation produced by chili peppers.

Q. Please explain the impact, hit or throat catch response.

A: This response occurs in the back of the throat, not in the mouth. In contrast to the irritation response it is immediate and short lived and occurs only during the inhalation of smoke.

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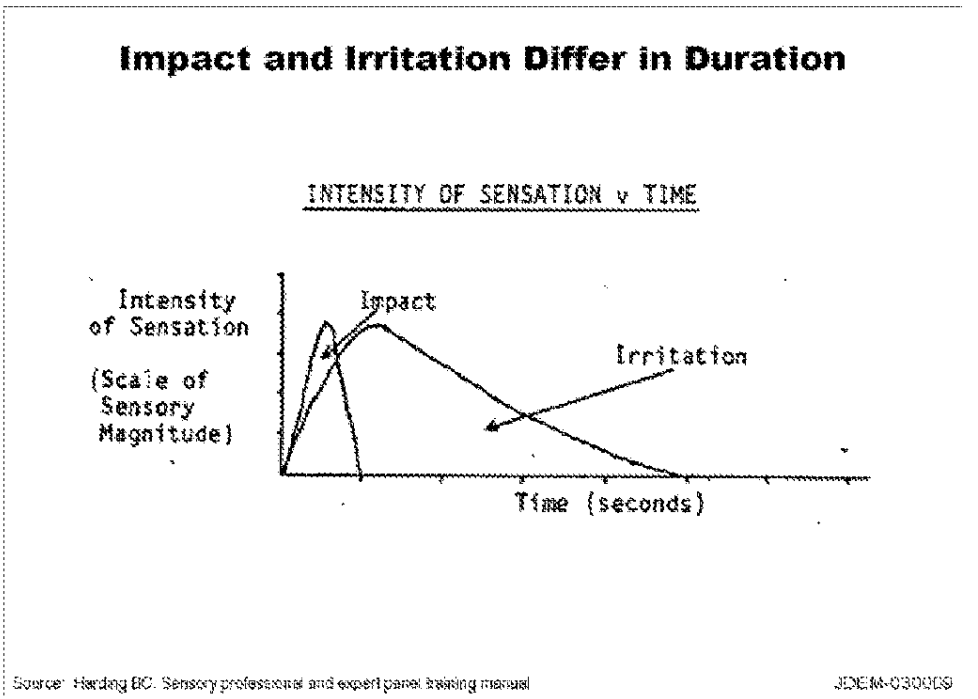

Q: What is JDEM-030009?

A: This is a graph from a BATCo R&D report that plots time against the intensity of effect. It demonstrates that the sensation of irritation is gradually built up and the sensation of impact is immediate and short-lived.

Q: Strength is not on your chart, is it a common chemical sense response?

A: Strength is not a separate sensory response. It is a combination of the irritation and impact characteristics of a cigarette. Sensory scientists break down the overall sensory response into its individual components whereas smokers tend to use less specific terms such as the strength of a cigarette when comparing different products. However, we have learned through our sensory research that smokers generally use the term strength to describe a combination of throat irritation and impact.

Q: Have the sensory properties that you have described been recognized by scientists outside of the tobacco industry?

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A: Yes for many years publications describing these sensations and their importance in smoking have been recognized. As early as 1922 there was a paper by Brill describing the sensory properties of smoke, using slightly different terminologies to those used today. More recently there was a paper presented by Dr. Bill Cain at the 1980 Banbury Conference on Safer Cigarettes. Cain described the importance of the sensory properties of smoke to the smoker.

Q: Do smokers describe the sensory properties of smoke in the terms you have described?

A: Smokers use these sensory properties to distinguish between different cigarettes. However, in everyday life smokers tend to use broad terms such as taste and strength. For example, a smoker may say they prefer the taste of one brand of cigarette or that another cigarette is too strong for their liking.

Q: How does nicotine contribute to the sensory properties of cigarette smoking?

A: It has very little contribution to taste (gustation), olfaction or mouthfeel. Nicotine's main contribution is to irritation and impact. In fact, as far as we know from our research it is the only component of smoke that will produce impact.

Q: In this trial, impact has been described in various ways. Dr. Benowitz testified that impact refers to a sensory experience that is produced in the afferent nerves in the back of the throat. Is Dr. Benowitz correct?

A: Yes. The afferent nerves Dr. Benowitz is referring to are sensory nerve endings in the back of the throat, and these are activated by nicotine upon inhalation. Nicotine gains access to those nerve endings as soon as the inhalation occurs. Those nerves send a signal immediately to the brain. These nerves conduct signals that travel at a rate of between twenty to forty meters per second. So the signal for impact reaches the brain in a fraction of a second after inhaling cigarette smoke.

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Q: In his testimony submitted to the Court, Dr. Wigand described impact as associated with the "nicotine rush" to the brain. Is impact associated with a nicotine rush to the brain?

A: No, impact is different. It is not related to pharmacological properties of nicotine in the brain – and it certainly isn't associated with "a nicotine rush" to the brain.

Q: Could you explain that?

A: To understand the difference, I have to explain that physiologists and pharmacologists draw a very sharp distinction, and an important distinction, between peripheral effects and central nervous system effects. A stimulation of sensory nerve endings in the body, while recognized of course in the brain, is a peripheral sensation. And it doesn't matter whether the stimulus is stubbing your toe, eating a chili pepper or activating the nerves in the back of the throat with nicotine. Central nervous system effects are the result of the direct activation in the brain by a blood borne substance. Nicotine causes both effects. The sharp immediate sensation of impact in the back of the throat is a peripheral effect, which is easily identified and described. The central nervous system effect of nicotine, which is the result of the delivery of nicotine through the blood to the brain is a totally different sensation, much more indefinite and subtle, and occurs gradually.

Q: How long has BATCo used the word impact to define the peripheral sensory effect in the back of the throat?

A: Since the early 1960s when BATCo's R&D adopted definitions for certain sensory responses. Since that time the definition has been consistently applied by researchers in R&D as seen in US 47,966.

Q: Did B&W ever have a different definition for impact?

A: Not to my knowledge and certainly not during my tenure at BATCo. The R&D reports from B&W use the same or very similar definition of impact to that used by BATCo and other tobacco companies.

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Q: At the time Dr. Wigand was at B&W, would he have had access to R&D reports describing impact and setting forth what it means?

A: Well I know that he had access since I wrote a number of research reports discussing impact and its relationship with nicotine that were sent directly to Dr. Wigand.

Q: Do knowledgeable scientists outside the industry use the term impact as BATCo defines it or as Dr. Wigand described it?

A: They use the same definition as BATCo.

Q: And can you give us some examples of that?

A: Pankow in his 2001 publication (JD-031642) and of course Dr. Benowitz has used the same definition in this trial and in some of his publications that I am familiar with.

Q: You testified that smoking mechanics and the sensory responses are related to the design of the cigarette and to the consumer acceptability of the cigarette. How do smoking mechanics relate to the design and consumer acceptability of cigarettes?

A: There are a number of design features that are related to smoking mechanics but the most important one is the pressure drop of the cigarette or what some call resistance to draw. If the resistance to draw is either too high or too low, the cigarette will not be acceptable to consumers.

Q: How are the sensory responses related to design?

A: There are many design features that directly affect the sensory properties and the acceptability of cigarettes. One of the most important is the amount of smoke that the cigarette delivers to the smoker. All of the sensory properties are affected by the amount of smoke, the less smoke delivered to the smoker the lower the overall sensory response. The type of tobaccos used as well as certain added flavour

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ingredients may also have effects on the various sensory properties. But one of the major determinants of a consumer acceptable product is overall smoke balance.

Q: What do you mean by smoke balance?

A: The sensory response produced during the puff must be in balance with the sensory properties perceived during the subsequent inhalation. Mouthfeel should be in balance with impact, and be in line with the consumers' expectations. In some markets consumers prefer a higher impact to mouthfeel balance. For example, U.S. smokers prefer blended cigarettes, which because of the tobaccos used, provide greater impact than flue-cured cigarettes of similar tar yields. However, U.K. smokers tend to prefer the flue-cured cigarettes. Smokers in some regions of Africa prefer cigarettes containing fire-cured tobaccos, and these have a very high impact to mouthfeel balance that would be entirely unacceptable to the majority of U.S. or U.K. smokers.

Q: Are those differences in impact and balance achieved by using tobaccos with higher levels of nicotine?

A: No. One could do that, and blended cigarettes do have a slightly higher nicotine content than flue-cured cigarettes, but mainly the differences in impact are due not to the amount of nicotine but to the form of nicotine and its availability to be absorbed into the upper airways at the site of location of the afferent nerve endings responsible for eliciting the impact sensation.

Q: How does the importance of peripheral sensory properties of nicotine compare to the central nervous system properties in terms of consumer acceptability?

A: When we look at consumers, and when we test cigarettes amongst consumers, we really have no way of measuring central effects of nicotine. We do have ways of measuring the peripheral sensory effects of nicotine, and these are included in our routine product evaluation procedures conducted in both 'in-house' sensory panels and external consumer assessment tests. We have developed a standardized system for defining and scaling the sensory properties of smoke, and this is used to train

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sensory panels to uniformly identify and subjectively quantify the sensory properties of cigarettes. That provides us with a means of distinguishing between brands and also allows us to make determinations of what makes one brand more acceptable than another. These panel assessments are very important to our ability to compete in the market place. Despite the importance of these assessments, we have not included any questions or panel training about the CNS effects of nicotine. That is because the CNS effects are not amenable to panel assessment particularly when one makes product assessments amongst consumers. Moreover, whilst there are different factors that can affect the degree of impact and other key sensory responses produced by a cigarette, the CNS effects of nicotine are probably simply related to the amount of nicotine delivered by the cigarette.

Q: Dr. Dixon I would like to now ask you some questions about a different topic, compensation. Compensation has been defined in different ways during the trial. How do you define compensation?

A: In my research and publications I have defined compensation as the modification in smoking behavior that occurs when smokers switch between cigarettes with different tar and nicotine yields as measured by standardized machine tests such as the FTC or ISO test methods.

Q: How does your definition of compensation compare with that found in Monograph 13 (US 58,700)?

A: In Monograph 13, Dr. Benowitz defines compensation as the degree to which proportional changes in a smoker's intake of a smoke constituent make up for the same proportional change in the machine-determined yield of that constituent. Dr. Benowitz's definition incorporates the same definition that I use and goes further to define how the degree of compensation may be expressed, using a mathematical formula. Dr. Benowitz is explaining that the degree of compensation is the degree to which smoking behavior modifications will reduce the proportional change in the machine measured intake of a given smoke constituent.

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Q: In this trial, Dr. Henningfield has referred to compensation as achieving more tar and nicotine from a cigarette than the FTC test would predict. What is your opinion of that definition of compensation?

A: That is not a definition of compensation in my view, nor is it the result of compensation. A person could change from a high yielding tar and nicotine cigarette as measured by FTC or ISO standards to a low yield cigarette and get more than the FTC or ISO measured tar and nicotine with no compensation.

Q: Can you explain?

A: Yes. Assume that we have a situation where a smoker is smoking a cigarette that has a 10 milligram standard FTC yield and he gets 20 milligrams of tar from that cigarette. Let's assume that our hypothetical person switches to a cigarette that has a 5 milligram FTC tar yield and he gets 10 milligrams of tar from that cigarette. In that hypothetical the smoker is not compensating. The proportional difference in the FTC yields of the two cigarettes is 50%, and the proportional difference in the tar obtained by the smoker is the same, i.e. 50%. In this instance there is no compensation, even though the smoker is getting more tar than the cigarette delivered in the FTC tests.

Q: Is that consistent with the definition of compensation as used in Monograph 13?

A: Absolutely. Monograph 13 compares the proportional change in the FTC measured yield to the proportional change in the delivery to the smoker, and if the two are the same there is no compensation.

Q: Can you give us an example where there is complete compensation?

A: Yes. Using the same hypothetical if the smoker got 20 milligrams of tar from both the 10 milligram and 5 milligram FTC rated cigarettes, then compensation is complete. Zero and complete compensation are the extremes, and the degree of compensation can fall between these extremes. This is defined as incomplete or

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partial compensation. With incomplete compensation a smoker would experience a reduction in tar intake following a switch from a higher to a lower yield cigarette but the reduction would not be the same proportion reduction as that produced by the FTC method. This is illustrated in JDEM-030028.

Q: Is there such a thing as a compensation index?

A: Yes.

Q: What is it?

A: A compensation index is a simple mathematical formula which allows you to calculate the degree of compensation. The degree of compensation is the difference between the proportional change in the delivery of the cigarettes when smoked by human smokers compared to the proportional change in the machine measured yields.

Q: Are there different ways to modify smoking behavior that have been suggested to compensate for the changed delivery of cigarettes?

A: Yes. As described in JDEM-030010, a number of different mechanisms have been suggested and researched over the years. These include: 1) changing cigarette consumption, i.e., number of cigarettes smoked per day; 2) changing the inhalation pattern, inhaling deeper or holding the smoke in the lung longer; 3) increasing the puff number by taking more frequent puffs or by smoking the cigarette farther down the rod; 4) blocking the filter ventilation holes with fingers or lips; and 5) increasing the size of the puff, i.e., increasing puff volume.

Q: Starting with cigarettes per day, what does the research show about that as a means of compensation?

A: Well, our own research shows it is certainly not a major factor in compensation. This is the case even in those experimental studies where cigarettes are provided to the participants free of charge. It is also consistent with most of the published research on the mechanisms of compensation including the conclusion reached in

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the 1984 Surgeon General's Report and also the conclusion from a fairly recent comprehensive review of research on compensation published in 1999 by Dr. Gerhard Scherer. JD-000547.

Q: How about inhalation, has that been researched as a compensatory mechanism?

A: Yes it certainly has. Although inhalation patterns are a little tricky to measure, studies have examined this issue and have consistently shown that people do not change their inhalation pattern when switching from higher to lower tar and nicotine cigarettes. Indeed, the 1984 Surgeon General's Report (US 64,059) reached the same conclusion about inhalation patterns and compensation. ("Smokers who switch from higher to lower yield cigarettes show compensatory changes in smoking behaviour, the number of puffs per cigarette is variably increased and puff volume is almost universally increased, although the number of cigarettes smoked per day and inhalation volume are generally unchanged.").

Q: What are the ways that people have postulated that inhalation could result in compensation?

A: People have suggested compensation may occur by increasing the depth of inhalation thereby increasing nicotine absorption in the deeper portions of the lung.

Q: Has there been research done on that postulation?

A: Yes, there has.

Q: What does it show?

A: Firstly, research published in the 1970s by Dr. Armitage, a pharmacologist at the TRC labs, in the U.K., (JD-011695) showed that most of the nicotine present in the inhaled smoke is deposited and retained within the lung during the inhalation process. Zacny and co-workers published the results of a very elaborate study in 1987 (JD-063009) in which they discovered that increasing inhalation depth from

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10% to 60% Vital Capacity did not result in an increase in the amounts or speed of nicotine absorbed into the systemic circulation.

I also recently co-authored a publication with Dr Armitage in which we looked at this very issue by conducting a detailed examination of the relationships between inhalation depth and the amounts of nicotine retained in the lung and subsequently absorbed into the blood during and following cigarette smoke inhalation. We controlled the inhalation depths of smokers and we found that increasing inhalation depth from five hundred milliliters to a liter had no effect on either the amounts of nicotine deposited in the lung or on the amounts of nicotine absorbed into blood. I should also stress that the range of 500 to 1000 milliliters covers the range typically observed in smokers. Therefore, the depth of inhalation has no effect on the degree of compensation.

Q: Are there any other mechanisms that have been postulated for the effect of inhalation on compensation?

A: Yes. The other one is the duration of inhalation together with what is called the post inhalation breath hold.

Q: Could you describe that?

A: If a person is inhaling the smoke, they could inhale it quickly or they could inhale very slowly. At the end of the inhalation, they may pause before they exhale. That is what is called a breath hold. It may be a long or short pause. It's been postulated that the longer the inhalation duration and breath hold the more time there is for the absorption of nicotine. The paper I previously mentioned by Zacny and colleagues in 1987 also looked at inhalation time and breathhold. They showed quite clearly that changing the breath hold from zero seconds to fifteen seconds had no effect on the amount of nicotine absorbed. The nicotine was essentially entirely absorbed without a post inhalation breathhold. We also recently confirmed this finding in our 2004 Armitage et al. inhalation study. Therefore, on the basis of our own work

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and the research of others, we have concluded that inhalation is not a mechanism for compensation.

Q: The next suggested compensatory mechanism on your chart is increasing the puff number. What has the research shown on increasing puff number as a means of compensation?

A: There have been a number of compensation studies examining this issue. The results are inconsistent. Some studies show a slight increase in puff number. Some show a decrease, and many studies show no change. It is potentially a mechanism, but the research is unclear.

Q: What about smoking the cigarette farther down the rod than the FTC or ISO standards stipulate, what do the studies show about this as a means of compensation?

A: Research has recently confirmed prior studies that have demonstrated this is not a significant compensatory mechanism. A study of U.S. smokers of different products ranging from one milligram FTC yield up to about eighteen milligrams FTC yield demonstrates that the average butt lengths were very similar across this wide range of FTC yields.

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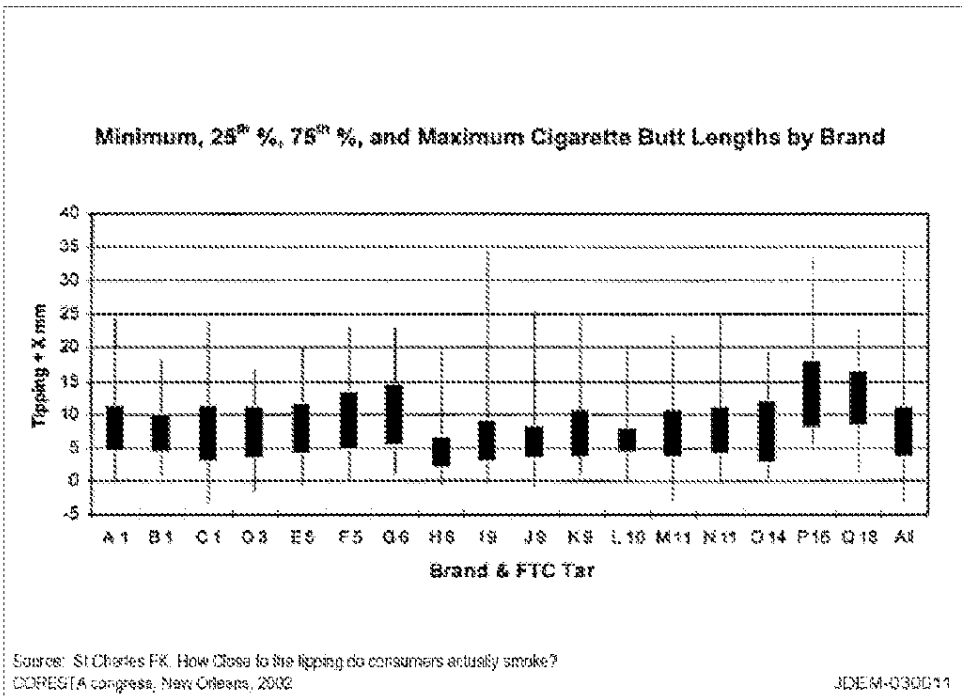

Source: St Charles FK. How Close to the tipping do consumers actually smoke? CORESTA congress, New Orleans, 2002

JDEM-030011

Q: What does this chart, JDEM-030011, show?

A: This is a graph from a study that one of my colleagues at Brown & Williamson conducted. On the graph, the x-axis is the cigarette FTC tar yield. The y-axis is the tipping plus millimeters of length in units of 5. The tipping is what is used to adhere the filter to the tobacco rod. The solid boxes represent the middle 50% of the smokers for each cigarette tested. Just looking at the first solid box on the far left of the chart, which represents the smoking behavior of smokers of a 1mg product, you can see that 50% of the smokers that smoked this product smoked to a butt length between 5 and 12 millimeters above the tipping paper. The whiskers, or thin lines above and below each solid box, represent the outer extremes of behavior among the smokers tested. What the chart shows is that there is no pattern of smoking farther down the cigarette as FTC yields decline. Therefore, the absence of the correlation between FTC yields and butt lengths demonstrates that smoking farther down the cigarette is unlikely to be a significant means of compensation.

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Q: Is blocking the ventilation holes in the filter another potential means of compensation?

A: Yes. It's been suggested that if a smoker were to either deliberately or inadvertently cover some of these holes with either their lips or their fingers this could obstruct some of the ventilation resulting in increased yields from the cigarette.

Q: Has that been researched?

A: Extensively.

Q: And what have the results of the research shown?

A: The conclusions drawn from the research have changed over the years. I think it's fair to say in the early 1980's researchers were suggesting that it could be a very important compensation mechanism. This was based on the sorts of techniques that were used at that time to try to assess the extent of hole blocking. Research in the late 1990s has shown that many of the techniques that were used in the 1980s were not as accurate as people originally thought. Today, according to chapter two of Monograph 13 (US 58,700) and the studies cited in it, ventilation hole blocking in light cigarettes is not a significant means of compensation. To the extent that ventilation hole blocking may be a mechanism of compensation, it is restricted to the very highly ventilated products, those using more than 65% ventilation.

Q: What type of cigarettes use that much ventilation?

A: Essentially the very lowest tar cigarettes, the one milligram tar products.

Q: What is the market share of those products?

A: It's very low. I believe that it is less than four or five percent in the U.S.

Q: Has BATCo performed research on the issue of blocking filter ventilation?

A: Yes, we've researched this and published the results of our research.

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Q: What have you found?

A: We found that the incidence of ventilation hole blocking is low and to the extent it occurs the consequences in terms of compensation are relatively insignificant for the vast majority of smokers.

Q: What did you find with respect to the incidence of filter hole blocking?

A: There are basically two ways to block holes. One way is with the lips. With lip blocking our research shows that approximately 15% of smokers have lip contact with the ventilation holes on one or more puffs. Finger blocking we found to be even more rare and 90% of smokers had no finger contact with the ventilation zone during the puff. I can give you the details of the research if you would like?

Q: No let's move on. I would like you to tell us what you found about the effects of hole blocking.

A: Yes. In our lip blocking study we obtained the filters from cigarettes smoked by the participants in the study so we were able to analyze those filters for nicotine content. We could then determine the amounts of nicotine delivered to the smokers from the cigarettes smoked during the study. So we analyzed the filters of smokers who showed no evidence of vent blocking and compared them with those smokers who demonstrated some degree of vent blocking. We looked to see if there was a difference between the nicotine deliveries in the non blockers versus the nicotine delivery in the blockers.

Q: What did you find?

A: We found a wide range of deliveries between the subjects but there was no difference between the blockers and non-blockers.

Q: Can you explain why that occurred?

A: There are two main explanations. First, we know from a number of published studies that neither fingers nor lips can block one hundred percent of the ventilation

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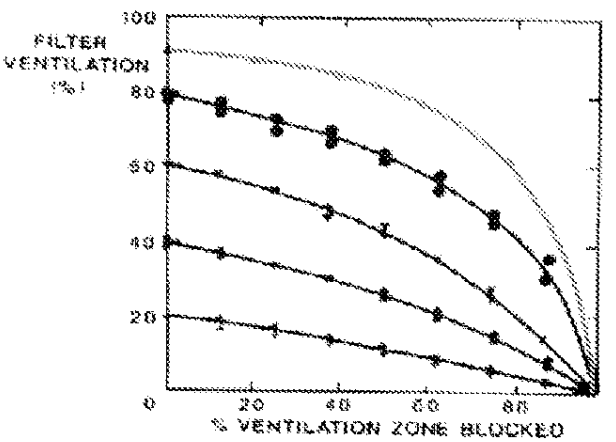
zone. And if you are taking out part of the ventilation the percentage of ventilation blocked does not result in an equal percentage loss of ventilation effects.

Effect of Partial Blocking of Ventilation Zone on Cigarette Filter Ventilation



Source: Tobacco Chemists' Research Conference, vol. 23, 1997 JDEM-030012

Q: What is this graph, JDEM-030012?

A: This graph came from a 1997 presentation made at the Tobacco Chemists Research Conference and shows the data from a study investigating the effect on ventilation from differing degrees of hole blocking. The y-axis is the percentage of filter ventilation and the x-axis is the percentage of ventilation zone blocked in the test. And you can see that the effect that blocking has on the ventilation is not linear.

Q: Using JDEM 030012, can you describe what effect partially blocking the filter ventilation holes had on the overall effect of ventilation?

A: As you can see from the chart, when you plot the degree of ventilation blocked against the degree of ventilation effect it is a fairly flat response until you get to extreme blocking situations. If you cover twenty percent or even fifty percent of the vent zones, that doesn't produce a twenty or fifty percent reduction in the amount of ventilation. We know from a number of studies, including studies

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published by Dr. Koslowski, the co-author of chapter two of Monograph 13, (US 58,700) and his colleagues, that even when people are asked to deliberately block as much of the filter holes as they can, with either their lips or fingers, the maximum area of the ventilation zone blocked was around 50 percent. You could see from the chart that even with fifty percent of the vent zone blocked, you still have ample ventilation to partially offset the loss from blocking. Additionally, in research we have conducted we have shown that partial blocking of the ventilation holes by smokers does not reduce the effect of deliveries to the same degree.

Q: Can you explain why it does not?

A: Yes. The explanation relates to the mechanics of the cigarette. When you introduce ventilation holes into a filter, that has the effect of reducing the resistance to draw of that cigarette. If you were to block some of these holes on the filter, that would cause the draw resistance of the cigarette to increase. And we know from a number of published studies including some of my own work, that if you increase the draw resistance of the cigarette, that has an effect on reducing the puff size. So in that situation, if you have a fair degree of ventilation blocking, that would cause an increase in the draw resistance of the cigarette and that would result in a reduction of the puff volume of the smoker. So the reduction of ventilation effect would be offset by the person taking a smaller puff. We have published our research demonstrating that. Zacny and colleagues also published similar work on vent blocking, resistance to draw and puff volume in their 1986 study.

Q: So in summary, doctor, what is your conclusion with respect to filter ventilation blocking as a mechanism of compensation?

A: My conclusion is that for the vast majority of cigarettes that are on sale in the U.S. market, even if you have ventilation hole blocking, smoke deliveries are not significantly increased. And for that small market of very highly ventilated cigarettes, hole blocking may be a means of partial but not full compensation.

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Q: Puff volume. You mentioned puff volume as a means of compensation. Could you explain what the research has shown with respect to puff volume?

A: There has been a lot of research and switching studies looking at the issue of puff volume and compensation. The science confirms that puff volume is the primary means by which smokers compensate. That is certainly my view as well as the view of the major reviews of the compensation literature.

Q: What are the factors that determine puff volume?

A: The one limiting factor on the puff volume is the size of the mouth. While there is obviously individual variability here, the maximum size of a puff will be approximately 100 milliliters. As far as the other factors that influence puff size, it was recognized fairly early on that the sensory properties of the smoke during the puff were likely to be the most important factors. As smokers smoke a cigarette it is common for them to decrease the puff volume as they smoke the cigarette down towards the filter. A typical example of the puff by puff volume responses in smoking is illustrated in JDEM-030013. This led to the hypothesis that it was either sensory properties of nicotine or tar that caused the change in puff size.

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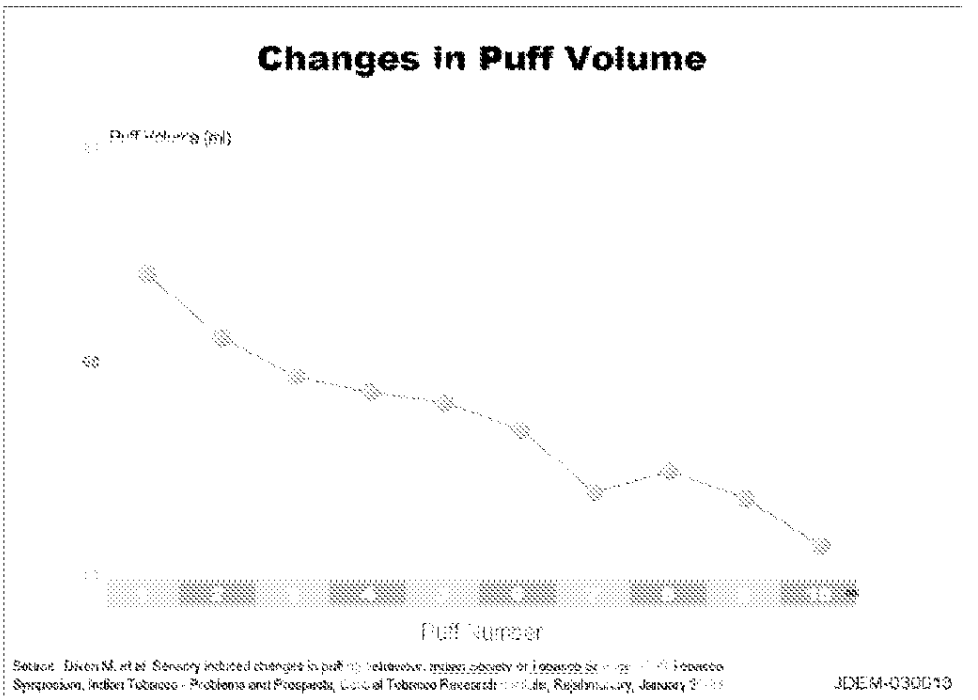

Q: Did you research the contribution of the sensory properties of nicotine and/or tar to puff volume?

A: Yes. We have conducted a lot of research on this issue. First, we looked at the hypothesis that nicotine satiation could be controlling puff volume. The theory at one time was that when a smoker first lights a cigarette, his or her needs for nicotine are at their highest and therefore the smoker takes a large puff. But then later on as nicotine builds up in the body, puff volume is decreased because the need for nicotine is satiated. However, by giving a group of smokers repeated first puffs on a number of cigarettes, we discovered that their puff volumes did not decrease with subsequent puffs and therefore we concluded that whilst nicotine satiation was clearly achieved in the study, it was not a controlling factor for puff volume as the chart summarizing some of the study's data shows. JDEM-030014.

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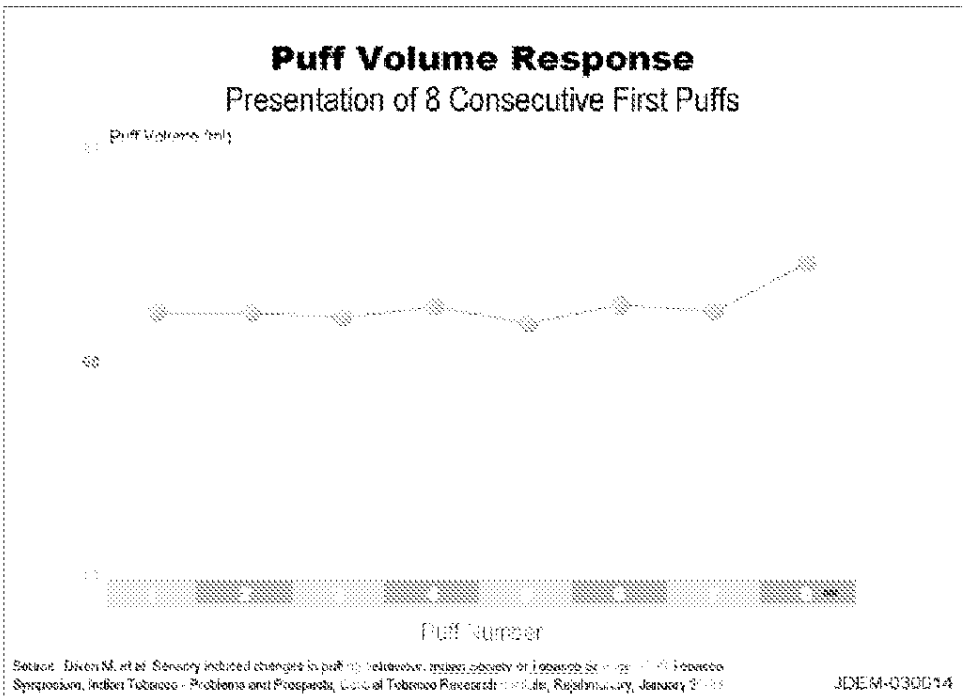

Q: Dr. Dixon, an expert witness for the government, Dr. David Burns, testified recently as follows:

> **"The second piece of information that's only come really clearly in focus in the last half decade or so was that the sensors in the back of the throat perceive nicotine as it comes out of the cigarette and send a signal to the brain that allows the smoker to adjust their [sic] pattern of smoking within that puff to increase or decrease the amount of nicotine they're getting and that they are going to get in their brain some seven or eight seconds later following ingestion into the lung"**

When Dr. Burns referred to "the sensors in the back of the throat that perceive nicotine," is he describing the afferent nerves responsible for the impact sensation?

A: Sounds very much like the impact sensation, but the throat does not perceive nicotine as it comes out of the cigarette. I hope I have made it clear by now that the smoke comes out of the cigarette and into the mouth during the puff and the throat is not in contact with smoke until after the puff is over and the smoke is inhaled. What Dr. Burns is describing in the testimony that you read to me is the

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production of an impact signal from the throat during the puff that would lead to adjustments in the puff size. Whilst it is theoretically possible that a person could draw smoke directly into the lungs without using the mouth it would be extremely difficult and would create a huge amount of impact and irritation that would be extremely unpleasant. What he is describing is simply not the way people smoke cigarettes.

Q: Dr. Burns went on in the same passage to testify as follows:

> **"That means that the changes that occur based on someone's addiction to nicotine are being modulated on a breath by breath – on a puff-by-puff basis within the cigarette being smoked by the smoker."**

Does the strength of the impact sensation experienced on inhalation, modulate the subsequent puff taken?

A: No, we did a study that addressed that issue. By giving smokers alternating puffs of light and regular cigarettes which would provide light and more intensive impact sensations, we found that the smokers did not change their behavior as you would expect they would do if impact was the response controlling puff size. Rather, the changes in puff size we observed were entirely consistent with changes in the sensory effects in the mouth during the puff, not with changes in effect during inhalation. As I've previously mentioned impact can only be sensed after a puff has been inhaled. After each puff of the regular cigarette, if impact was the controlling factor, the puff size of the subsequent puff should have decreased, and after each puff of the light cigarette the puff size of the subsequent puff should have increased. That is because the impact would be the greatest upon inhalation of the regular cigarette puff. In fact, as the summary in the chart (JDEM-030015) shows, the opposite occurred.

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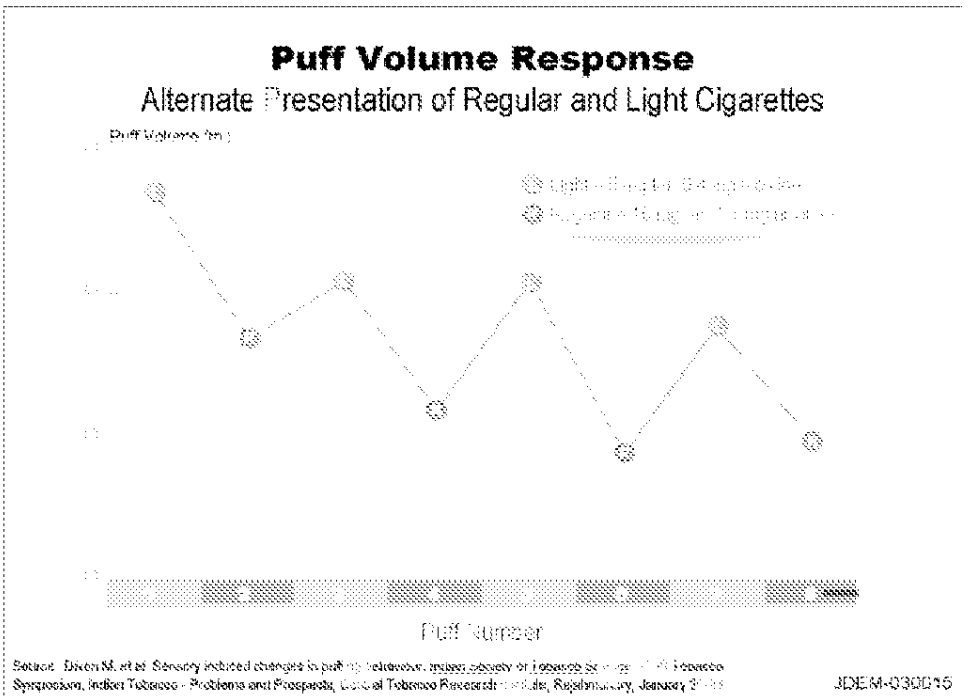

Q: What did you conclude as a result?

A: We concluded that tar, not nicotine, was the major factor influencing puff volume because the size of the puffs were entirely consistent with the sensory properties of the smoke in the mouth which is due to tar. This was further confirmed in work that we (JD-024497) and others (JD-062719) did where smokers were given cigarettes that were matched in tar yield, but delivered different nicotine yields. There was quite a big difference in nicotine yield. If the nicotine yield was controlling the puff volume, we would expect there to be a small puff with the high nicotine yield cigarette and a big puff with the low nicotine yield cigarette. What we in fact found was there was no difference between the two cigarettes. That led us to exclude nicotine as the controlling factor in puff volume.

Q: So what are the conclusions that you have reached about the controlling factors for puff volume?

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A: My conclusion from our own work (JD-024497) and from my review of external work (JD-062719) is that puff volume is controlled by the sensory properties of tar and that the most important property is mouthfeel.

Q: When did BATCo start looking at the issue of compensation?

A: It was really in the early 1970s when BATCo started investigating the concept of compensation.

Q: And do you know when the first published studies of compensation occurred in the U.K.?

A: The first, I guess, real compensation studies were again in the early 1970s. In 1970 there was a seminal publication by Ashton and Watson on compensation. JD-040302.

Q: Who funded that study?

A: It was funded by the U.K. tobacco companies through the Tobacco Research Council.

Q: What was the motivation for this early work?

A: Shortly before that time frame the U.K. Department of Health began investigating the idea that one way to make a less hazardous or less harmful cigarette would be to reduce the tar yield of that product. It became known as the tar reduction program or the low tar program in the U.K. At the time, lower tar and nicotine yield cigarettes were being proposed as a potential way forward to produce a less risky product. But it was recognized right at the outset that if the smokers compensated in an attempt to restore the nicotine intake from the low yield cigarettes, that would effectively increase the tar yield from the low tar cigarettes and seriously undermine the goals of the tar reduction program. This led many in the U.K. to suggest that tar yields should be reduced but nicotine yields should be maintained at levels typical of regular cigarettes.

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Q: When was this suggestion of reducing tar while maintaining nicotine first made?

A: I have seen evidence that this suggestion was made by the U.K. tobacco companies to the Royal College of Physicians as early as 1967.

Q: Was the idea pursued after 1967?

A: It was pursued for many years after 1967 and it's still being researched today. There are a number of tobacco health researchers who are still proposing this approach as a way forward to producing a safer cigarette.

Q: Have members of the U.K. public health community continued to encourage research to develop a lower tar maintained nicotine product until today?

A: Yes, for example in connection with the most recent European Directive on smoking a suggestion was made to place limits on the nicotine yields of cigarettes. The EU like the U.K. had limits on tar yields but there were no limits on nicotine. When the EU suggested limits for nicotine as well as tar it was opposed by a number of members in the public health community. This is in stark contrast to the approach that I understand has been taken in the U.S.

Q: Doctor, has BATCo researched ways to make lower tar cigarettes that would provide a compensating smoker with the nicotine that he or she wants?

A: Yes, they have. From the 1970's until the present time.

Q: How did BATCo research this issue of low tar maintained nicotine yield cigarettes.

A: BATCo began exploring using higher nicotine content tobaccos in the blends in order to change the nicotine to tar ratios of the product. Some of this work was done in conjunction with Michael Russell, a prominent nicotine researcher who was and is held in high regard by the U.K. public health community. Indeed, this whole idea of having a low tar, maintained or higher nicotine yield cigarette was

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often referred to as the 'Russell cigarette'. So BATCo scientists provided some experimental cigarettes for Dr. Russell to evaluate.

Q: What was the result of changing of the tar nicotine ratios with using a higher nicotine blend tobaccos?

A: It was possible to make a low tar and higher nicotine delivery cigarette. But the cigarette failed to achieve any degree of consumer acceptability. And we now believe the reason for the poor acceptability was the imbalance between the various sensory properties of the cigarettes, especially the imbalance between the low sensation of mouthful during the puff and the high sensation of impact during inhalation.

Q: Were there other research attempts pursued to try to create additional nicotine delivery to the smoker while lowering tar?

A: Yes. There was an attempt called Project Rugby. That project was based on a theory that if you were to change the smoking mechanics of the cigarette to allow smokers to obtain higher flow rates through the cigarette filter, this would, to a certain extent, alter the relative filtration effects for tar and nicotine and result in a higher nicotine to tar ratio in the smoke. This was an idea put forward by Colin Greig at BATCo in the 1980s. It was tried in the laboratory but it was determined that the nicotine to tar ratio change was minimal and there were a number of insurmountable problems with the design. It was never marketed and the project was abandoned.

Q: In his written testimony in this trial, Dr. Burns discussed a memorandum by Colin Greig, US Exhibit 20,230, that he said was an example of an attempt to develop products that could be promoted as delivering lower yields, but when smoked would deliver a full dose of nicotine in order to satisfy the smoker. Is the memorandum Dr. Burns is referring to in his testimony addressing the same project you just described?

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A: Yes. That memorandum is based on a talk that Dr. Greig gave in which he suggested that Project Rugby may produce a reduced tar cigarette that would allow the compensating smoker to derive the nicotine that he or she is seeking.

Q: Was Project Rugby an attempt to produce a cigarette that could be promoted as delivering lower yields that would deliver to the smoker nicotine that he or she is seeking as Dr. Burns' claims?

A: He is right in part. As I said this was an attempt to make a cigarette with a lowered tar to nicotine ratio through smoking mechanics rather that tobacco blends. And that is clearly set out in the memorandum. If it were possible to make the cigarette it would have been promoted as delivering less tar, which is what it was designed to do as smoked, but also provide more nicotine as was envisioned by the Russell cigarette. At the time of this memorandum, the U.K. government was progressively lowering the delivery of tar through a series of agreements with the industry, but these reductions did not apply to nicotine. Manufacturers had been encouraged just the year before this memorandum to research and develop lowered tar and maintained nicotine cigarettes by the Independent Scientific Committee on Smoking and Health. Project Rugby, the research discussed in this memorandum, was in direct response to the research request of the ISC.

Q: Turning again to compensation, what type of studies were used to investigate compensation?

A: Switching studies where you would take groups of smokers smoking a high tar and nicotine yield cigarette and then switch them experimentally to a lower tar and nicotine yield cigarette.

Q: Could you briefly review the methods used to assess compensation?

A: Early methods were observational methods, merely observing people to see if they changed their smoking behavior. Also fairly early on there was a technique developed to measure the amount of nicotine and tar remaining in the filters of smoked cigarettes to allow researchers to estimate the amounts of tar and nicotine

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delivered to the smokers. This was a useful technique because it allowed the researcher to estimate the tar and nicotine delivered to smokers as they smoked their cigarettes in their normal environments -- i.e., it didn't suffer from constraints imposed by conducting measurements in laboratory settings. However, it suffered from some serious limitations.

Q: What were those limitations?

A: There were a number of methodological problems. The main ones were artifactual condensation of nicotine on the filter and the fact that the technique relied on constant filter efficiency. However, research indicated that filtration efficiencies could vary under certain smoking conditions.

Q: Were there methods developed to try and circumvent these problems?

A: There were a number methods that were developed and used in compensation research. The next notable advance was the development of the puff recorder and smoke duplicator.

Q: What did this technology provide researchers investigating smoker compensation?

A: It provided the ability to measure puffing topography, i.e. the flow rate, the volume, the puff interval, duration of puff and the number of puffs, to allow the researcher to accurately characterize the way in which a smoker smokes a cigarette. In the original recorder developed in the 1970s, the puffing topography data was recorded on a tape that was played back through a puff duplicator machine. The duplicator smoked the cigarette in exactly the same manner as the smoker, and it enabled the researchers to capture and measure the same amount of tar and nicotine that was delivered to the smoker.

Q: I have handed you JDEM-030016. What is that?

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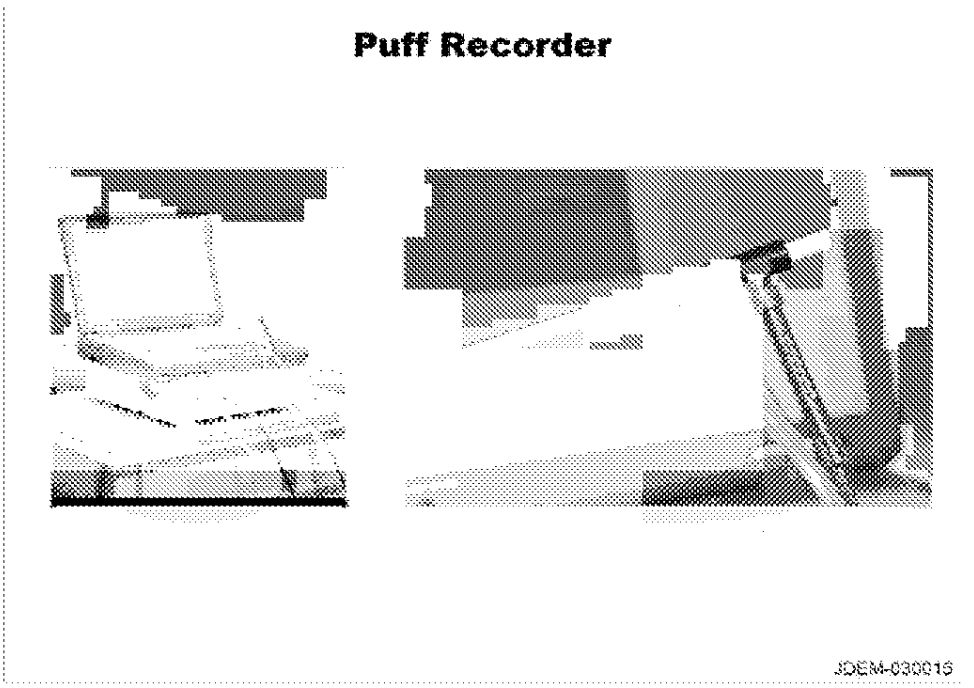

A: This is picture of one of today's puff recorders. At the end of the cigarette there is a small flowmeter that measures the flow-rates and pressures during the puff, and these are used to derive all of the puffing topography measures.

Q: Handing you JDEM-030017. What is that?

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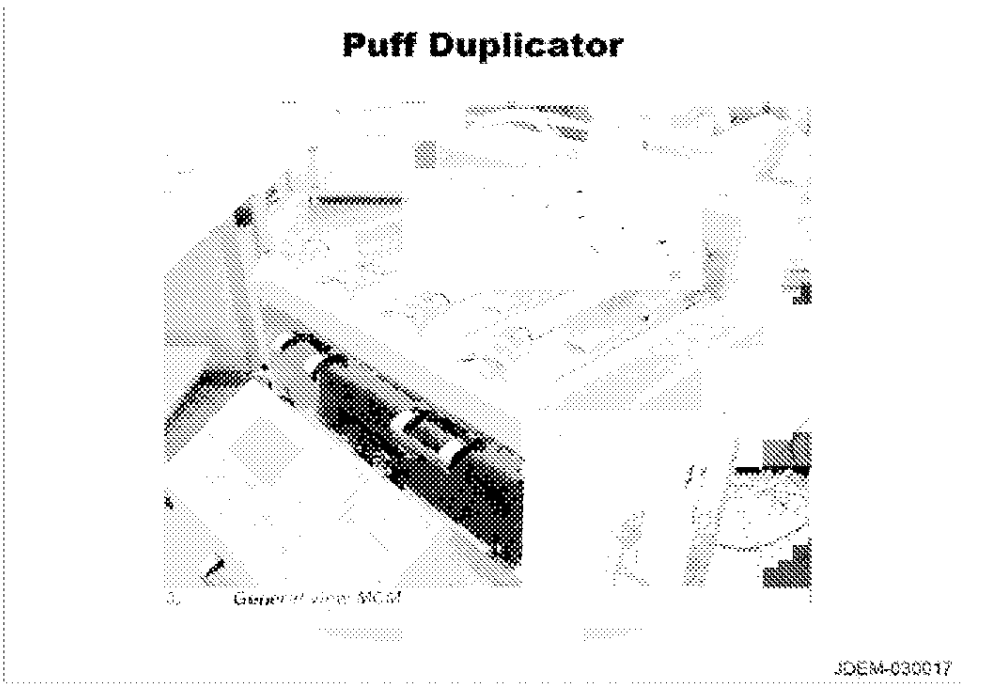
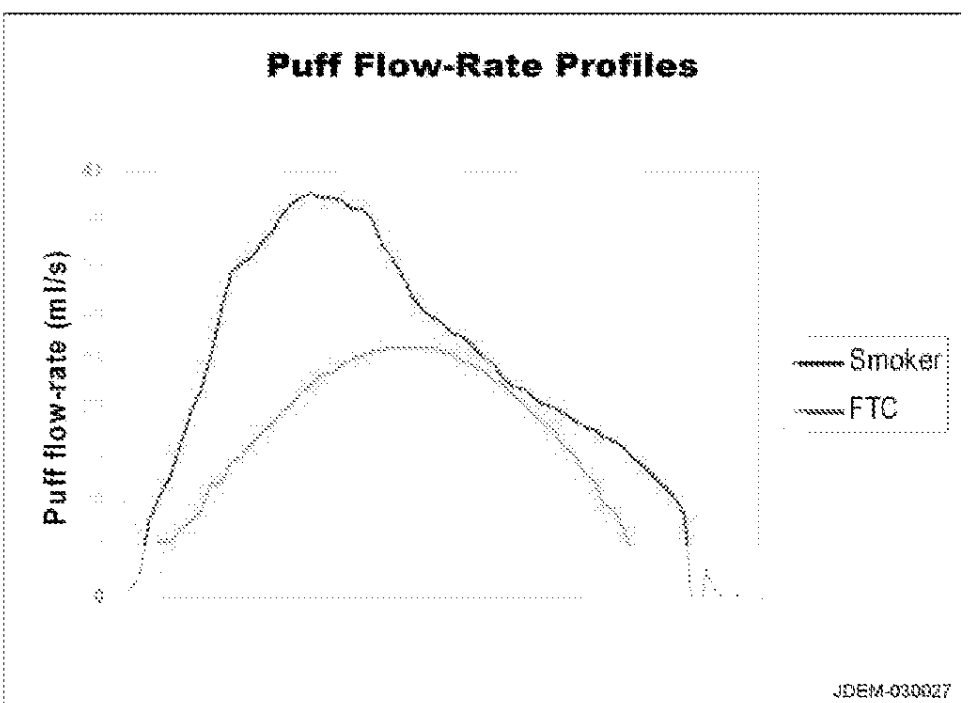


A: This is a picture of our most recent puff duplicator.

Q: And JDEM-030027?



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A: This is an example taken from thousands of topography recordings made at our Southampton R&D facility. It shows a puff profile taken from a smoker and compares it with a profile obtained from the standard FTC or ISO smoking machine.

Q: Who developed that equipment?

A: The tobacco companies, including BATCo, were some of the pioneers in the development of the recorder and puff duplicator. It was all published in technical journals and in the book Smoking Behavior, edited by a BATCo scientist, Ray Thornton, in 1978. (JD-010758).

Q: Was the puff duplicator and the instrumentation you have been discussing made available to people from the scientific community outside of the tobacco companies to assist in their own research on experiments with respect to compensation?

A: Yes, it was. Michael Russell, Rob Stepney and others were given access to this equipment to enable them to conduct their own experiments.

Q: Did that result in publications as well?

A: Yes, it did. JD-000383 and JD-010952.

Q: Are there limitations to the use of the puff recorder and duplicator in terms of measuring smoke compensation?

A: Yes, there are two major limitations. The first limitation is that the recording equipment requires each smoker to be monitored in a laboratory setting. This is a severe limitation because it doesn't allow us to study large numbers of smokers in field studies conducted in their natural environments. Moreover, it is well recognized that smoking research done in laboratory or clinical settings causes increases in smoking intensity.

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Q: There has been a lot of discussion in this case about the use of biomarkers for nicotine to measure compensation. When were these measures developed?

A: People started to look at nicotine levels in the blood around the same time that the puff duplicator was being developed. However, there were major problems with these early studies. Obviously this technique did not measure tar, it had to be estimated from the nicotine measurements. Additionally, and most importantly, the nicotine has a very short half life, approximately 2 hours, and quickly metabolizes into other substances. Therefore, it was extremely difficult to use this measure for meaningful switching studies. The technique was also invasive and had to be done in a clinical setting.

Q: Were there any other major techniques used for research on compensation prior to 1980?

A: No. There were a few other methods explored but they generally had more fundamental limitations than the ones we have discussed. Most were measures of neither nicotine nor tar and thus were less reliable measures of compensation than those I've previously discussed.

Q: Prior to 1980 what did the switching studies, using these various methods for measuring compensation show?

A: The book Smoking Behavior edited by Ray Thornton that I mentioned earlier (JD-010758), was the result of a conference of leading experts on nicotine. The conclusion of those experts at that conference, as reflected in the book, was that compensation did occur, but compensation was incomplete. My review of the BATCo research and the research in the published scientific literature also confirms that the overwhelming consensus before 1980 was that compensation, while universal, was invariably incomplete.

Q: What was the next major development in compensation research after 1980?

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A: The next major advance was the development of cotinine as a biomarker of nicotine in the blood. This technique was set out in a paper by Neal Benowitz and others in 1981. Cotinine, which is a metabolite of nicotine, has the advantage that it has a long half life of 16 hours or more and allows for measures of daily nicotine intake that can be used in switching studies.

Q: Are there limitations to using cotinine as a measure of compensation?

A: Yes. Cotinine is derived from nicotine and as such can provide an indication of nicotine exposure but not of exposure to tar. Secondly, cotinine whilst being the major metabolite of nicotine for most individuals is not the only metabolite of nicotine. This is very important because of the large inter-individual variation in the rate of nicotine metabolism to its various metabolites, and the distribution and clearance of nicotine and its metabolites from the body. US 64,226 (Interindividual Variability in the Metabolism and Cardiovascular Effects of Nicotine in Man). You can have two individuals who have exactly the same nicotine intake but one person could have a level of cotinine in the blood which is three times higher than the other person. Whilst this significant inter-individual variation in nicotine metabolism to cotinine is a serious limitation in the interpretation of cross sectional studies, it may not be a major limitation in switching studies investigating compensation because individual smokers are used as their own controls in switching studies.

Q: What do you mean by cross sectional studies?

A: A cross sectional cotinine study is basically a snap shot of what the cotinine levels are in smokers smoking their usual brand of cigarettes. It provides no direct information about compensation because smokers are not switching from one cigarette yield to a different yield of cigarette.

Q: Why is the variation in metabolism of cotinine a major limitation in a cross sectional study but not necessarily in a switching study of compensation?

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A: That's because in a cross sectional study you are using cotinine to compare the nicotine intake of one smoker to another and that comparison may be three times different than a comparison of the actual nicotine intake because of differences in metabolism between the smokers. In the switching study, the same smoker is used to compare differences in smoke intake between high and low yield cigarettes. Thus, the variation between individuals is not a factor.

Q: Have cotinine biomarkers been used in switching studies to measure compensation?

A: Yes, there have been at least 13 such studies since 1980.

Q: What do these studies show with respect to compensation?

A: Most of those studies show that some degree of compensation occurred when people switched from high to low yield products. Those studies generally show that compensation was incomplete.

Q: Has there been an attempt to summarize the results from these various switching studies examining biomarkers of nicotine?

A: Yes, there was a comprehensive review of the compensation literature published by Scherer in 1999. (JD-000547). Based on the nicotine biomarker data in the studies reviewed, Scherer calculated a compensation index for each study. A meta analysis of these indices, published in the review, demonstrated a mean compensation index of around 60%.

Q: Turning to Monograph 13 (US 58,700). Were there any switching studies using biomarkers cited or discussed in chapter 3 of Monograph 13 entitled Compensatory Smoking of Low Yield Cigarettes that were not included in Dr. Scherer's meta analysis?

A: Yes. There were three such studies.

Q: And have you reviewed all three studies?

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A: Yes.

Q: What are they?

A: There was a study by West, which is covered in Monograph 13. One by Russell and colleagues in '75 and then there was the one by Lynch and Benowitz, which was referred to as a spontaneous switching study in Monograph 13.

Q: Now, looking at the West study, was there data available in that study to derive a compensation index as Dr. Scherer did with the other biomarkers he reviewed?

A: Yes. Using the data in the West paper, I calculated the compensation index to be approximately 30%.

Q: How does that compare with the compensation index Dr. Scherer calculated from his meta analysis?

A: It is lower.

Q: If the West paper had been included in Dr. Scherer's analysis what would have been the result?

A: Since the degree of compensation reported in the West study was less than the average, or weighted average, of the studies reported by Scherer, it would reduce the average degree of compensation and would reduce the compensation index if included.

Q: How about for the Russell study in 1975, was there data that would provide enough information to allow the calculation of a compensation index?

A: Yes, there was.

Q: And did you review that and determine what the compensation index would be?

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A: Yes. In fact, Dr. Benowitz did that for us in Monograph 13 where the compensation index was twenty percent.

Q: How does that compare with the meta analysis of Dr. Scherer?

A: It's much smaller compensation index than the average reported by Scherer.

Q: If Dr. Russell's study had been included in the Scherer's meta analysis, what would have been the result?

A: It would have reduced the average or weighted average level, not by a huge amount because it's a relatively small study. But the mean compensation index would have been slightly less.

Q: That leaves the Lynch and Benowitz study. Did that study provide data that would allow one to compute a compensation index from the data provided?

A: Yes it did.

Q: And have you looked at that and did you compute a compensation index?

A: Yes, I have gone back to the original paper. And I calculated a compensation index. It's around fifty percent.

Q: How would that compare to the meta analysis of Dr. Scherer?

A: Again, it's lower.

Q: If that study had been included in Dr. Scherer's meta analysis, what would have been the result?

A: It would have brought down the mean value for the compensation index reported by Scherer.

Q: What conclusion can properly be drawn from the switching studies using nicotine biomarkers?

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A: Compensation occurs but it is incomplete.

Q: In sum, Dr. Dixon, do you have an opinion about what conclusions could properly be drawn about compensation from all of the published research and the internal tobacco company research that you have reviewed?

A: Yes, in my opinion the overwhelming consensus of the research using different methodologies and different populations leads to the fundamental conclusion that whilst compensation occurs it is invariably incomplete. Smokers who switch from higher yielding cigarettes as measured by FTC or ISO testing methodologies reduce their intake of tar and nicotine.

Q: Turning from compensation to a different, but related subject. There has been a fair amount of testimony in this trial about the FTC testing method and how it relates, if at all, to how smokers smoke cigarettes. Was the FTC methodology designed to predict what a smoker would get from a cigarette?

A: No.

Q: What was the purpose of the FTC test methodology?

A: The purpose of the FTC test was to have a method of measurement to enable products to be ranked by their deliveries measured using a standardized method.

Q: Was the utility of the FTC method for this purpose analyzed in the mid 1980s?

A: Yes. One of the major reviews that I am aware of occurred at the Scarborough Conference in 1984. This was an international workshop held in the US to examine the policy adopted in many countries to reduce tar yields.

Q: What was the conclusion of the conference?

A: The consensus opinion of those at the workshop was that the policy had been beneficial and that tar yields should be further reduced. JD-000867.

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Q: Did the conference examine the relevance of tar yields based on a standard set of machine smoking variables?

A: It did, and the conclusion of the conference was that standardized machine measures, such as the FTC method, did provide useful information on the ranking of cigarette brands by yield.

Q: Subsequent to that, have there been other attempts to review and look at this issue?

A: Yes. There have been a number of conferences aimed at looking at the relevance of the FTC method. For example, over in the U.K. the Independent Scientific Committee on Smoking and Health undertook a detailed examination of the relevance of the ISO method and concluded that the ISO standardized test method, which is very similar to the FTC method, did provide relevant and useful information on the yield rank order of cigarettes to consumers.

Q: Was it also looked at in Monograph 13?

A: Yes, Dr. Benowitz reviewed this in Chapter 3 of the Monograph.

Q: What did Dr. Benowitz rely upon to assess the relevance of the FTC rank order of cigarettes to the deliveries smokers get from cigarettes?

A: It appears that Dr. Benowitz relied heavily upon a number of cross sectional studies where smokers provided urine samples or blood samples and the nicotine metabolite cotinine was assessed. From those he constructed a relationship between the nicotine intake based on the metabolites versus the FTC nicotine rating.

Q: What did these cross sectional studies show?

A: Most of the studies showed there was a relationship between nicotine intake and FTC yields, i.e., they were positively correlated. That means that there were trends towards cigarettes with high FTC yields being associated with the higher intake

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and those with lower FTC yields being associated with the lower intake. But the correlation was weak. This is not surprising given the high degree of inter-individual variation that occurs in cross sectional studies that use cotinine as a biomarker of exposure. Firstly, as recognized by the FTC in 1967, smokers vary widely in their smoking behaviour patterns. Thus one would expect a wide inter-individual variation in nicotine intake at each of the points on the FTC nicotine yield continuum. Such a wide natural variation would result in a marked reduction in the correlation between FTC yields and nicotine intake. Secondly, as I explained earlier, the inter-individual variation in the metabolism of nicotine to cotinine also limits the ability to accurately compare the actual intakes of nicotine deliveries for different smokers by the use of cotinine measurements in cross sectional studies. Additionally, there are other problems with using cross sectional studies as a measure of smoke intake. By their nature they generally involve body fluid sampling in the clinic and the clinical aspect of a study may influence the behaviour of the participants. Also if the biomarker studies are used to interpret nicotine deliveries on a per cigarette basis, they have to rely upon self reported cigarette consumption which whilst providing a 'ball-park' figure is not sufficiently accurate for such derivations.

Q: Do these cross sectional studies provide a definitive answer to the question of whether or not the FTC rank order of tar deliveries of cigarettes provides valid information to the consumer?

A: I don't think it gives a definitive answer.

Q: Why not?

A: A number of reasons why not. First, I have already explained the limitations of the cross sectional studies for comparing the actual intake of nicotine among smokers. Additionally, and importantly when discussing FTC tar rankings, none of these studies measure tar intake. Whilst it is possible to infer something about tar yield from the tar and nicotine ratios of the cigarettes we know that these ratios are not constant and can vary according to changes in smoking patterns. Also, we know

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from the studies on compensation, that smokers do reduce their exposure to tar and nicotine when they switch from a cigarette with a higher tar and nicotine yield to a lower yield cigarette which is consistent with the rank ordering of cigarettes by FTC yield.

Q: Are you aware of attempts by public health authorities to look at the issue of the correlation between the ranking of cigarettes according to standardized test methods and actual deliveries to smokers?

A: Yes I am.

Q: Could you tell us about that?

A: Well, one example, in Europe, we have what is called the Tobacco Product Directive. Part of that directive sets maximum limits on tar delivery and these can be reduced periodically. Those deliveries are measured using the ISO system which in effect is almost the same as the FTC method. The last EU Product Directive which was implemented about two years ago continued the policy of reducing tar yields from the previous maximum of 12mg down to the new ceiling of 10mg as measured by the ISO method. Although the tar yield policies in this and previous EU Directives were based on the ISO method, a suggestion was made that we ought to look more closely at the relevance of the ISO method and determine if the ISO method needs to modified or whether new methods could be introduced to replace the current ISO method. Very recently, representatives from the WHO and ISO organizations have met and a working party of scientists has been established to look at the ISO measurement issue. One of the key tasks of the working group will be to obtain as much information as possible on the amounts of tar and nicotine smokers obtain from cigarettes in order to relate these amounts to the ISO values or to the amounts obtained from modified ISO tests or any new measurement procedure. Ultimately the working group will be in a position to recommend either the continuation of the current ISO method or the adoption of an alternative method.

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Q: Have you been invited to become a member of that committee?

A: Yes.

Q: Has BATCo investigated this issue of the relationship between FTC or ISO tar and nicotine yields of cigarettes and what yields smokers actually get when smoking their cigarettes in their natural environment?

A: Yes, we have.

Q: And how have you done that?

A: We have developed a noninvasive method which relies on the analysis of the used filters collected from large groups of smokers.

Q: Is this the old filter analysis that you described was used in some of the early compensation studies?

A: No, it's not. That old methodology would not do that job. There were too many deficiencies. What we have done in the last two or three years, is to take the old filter analysis method and modify it in such a way that the previous major concerns about the inaccuracy of that method are rectified. Earlier on I mentioned things like changes in filtration efficiency caused by changes in puff flow rate, and the problems caused with condensation into the filter. We now have a way of eliminating or virtually eliminating those problems. So our method which we have developed in the last couple of years we believe is a much more robust method than the former. And it gives us a direct measure of both the tar and nicotine from each cigarette the person smokes.

Q: Has this methodology been validated?

A: Yes, it has.

Q: And how did you do that?

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A: We validated the method by using our human puff recorder and puff duplicator. We took a group of smokers and we got them to smoke a whole range of cigarettes, ranging from the highest yield down to the lowest yield. These cigarettes had many design differences including different blend styles, filtration efficiencies and levels of filter ventilation. We recorded the puff profiles from the cigarettes when smoked by the smokers and these were played back through the smoke duplicator. This process provided us with the exact amount of tar and nicotine delivered by that cigarette under human smoking conditions. And we then took the spent filters from those very same cigarettes used in the duplication process and we used our new filter analysis method to estimate the tar and nicotine deliveries produced from those human smoking profiles. As shown in JDEM-030019, we then compared the results from our filter analysis method to the actual values obtained by using the puff duplicator. When we did that, we found a very good relationship between the deliveries obtained by our filter analysis method and the actual deliveries obtained from the duplicator.

JDEM-030019 shows the results for the validation study for the tar yields ("NFDPM"). The x axis shows the actual tar yield obtained from the smoke duplicator and the y axis is the estimated tar yield from our filter analysis method. There is an excellent agreement between estimated and actual tar yields.

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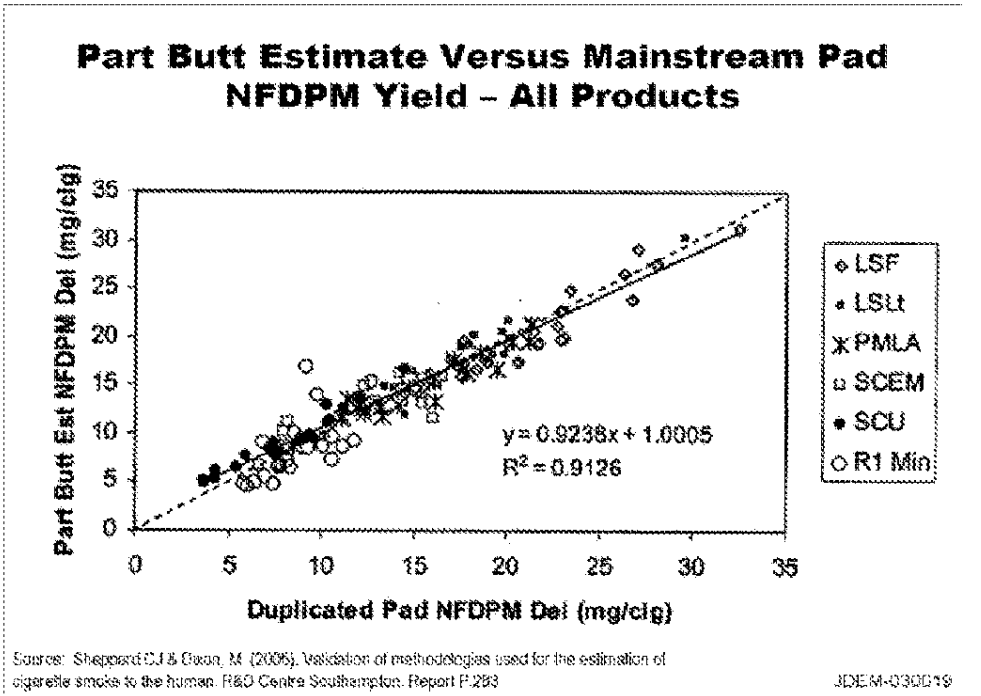

Q: Now, have any attempts been made to correlate yields obtained using this new methodology with biomarker studies?

A: Yes, some of my colleagues did a clinical study comparing the nicotine yields as measured by our filter analysis method with nicotine intake estimated from the levels of nicotine and five metabolites of nicotine in 24 hour urine collections. It was a week long clinical study involving about 75 smokers smoking their usual brand of cigarettes with yields ranging from the lowest to highest FTC yields.

Q: What did that show?

A: It showed a good correlation between the nicotine yields estimated from filter analysis with the nicotine uptake estimated from the nicotine biomarkers in urine.

Q: Let me show you JDEM-030020.

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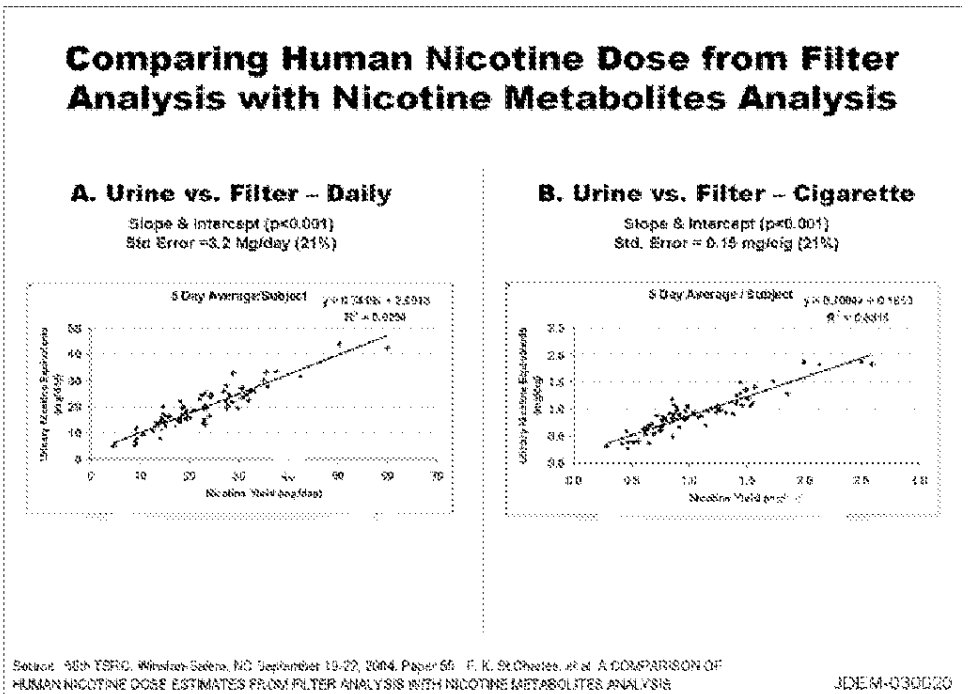

A: These are graphs of the correlation between the yields derived from filter analysis and biomarkers. On the first chart -- "A. Urine vs. Filter - Daily," the daily nicotine metabolites averaged over a 5 day period are plotted on the y axis and the daily nicotine yield as measured by filter analysis is plotted on the x axis. The chart to the right, is a similar chart based on per cigarette measures. As you can see the correlation for both is excellent. Although we also had measures of tar from our filter analysis it is not included on these charts since there was no direct measure of tar possible with biomarkers.

Q: Have you used this new analysis to examine what smokers get in their natural environment?

A: Yes. We are able to do that with our filter analysis method and have conducted a large representative study of smokers in the U.S.

Q: How many people were involved in this analysis?

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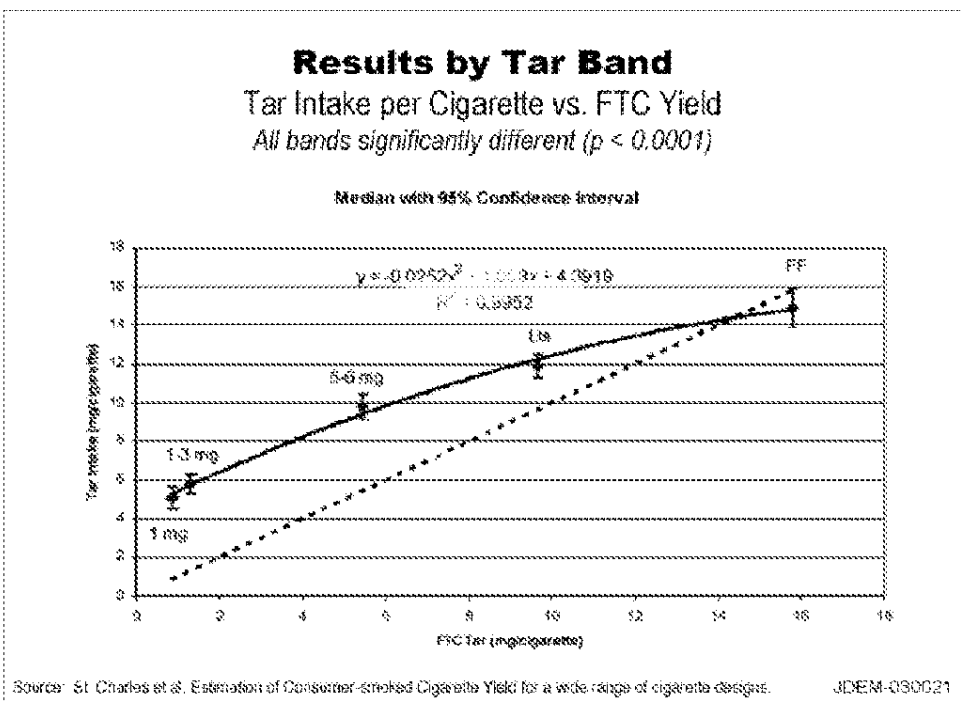
A: Roughly 800 smokers from different cities in the US. They were smokers of cigarettes with FTC yields ranging from the lowest to the highest yields on the market today.

Q: What did the study show?

A: The results of the study are depicted in this chart JDEM-030021. We analyzed the data from our study in four tar bands and as you can see there is a good relationship between FTC tar yield and human tar intake per cigarette. The full flavor products produce the highest and the ultra low products the lowest tar deliveries to the smokers.



Q: Has this data been presented publicly?

A: Yes.

Q: Where has that happened?

A: It was presented at the Tobacco Science Research Conference two years ago, I believe. It was also presented at the CORESTA Congress the same year. We have

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also presented aspects of this data to some health authorities, including representatives from the Swiss health authority and the New Zealand health authority.

Q: Are there plans in the future to publish these results?

A: The validation study comparing the puff duplication and filter analysis and the correlation study comparing the results of filter analysis and biomarker data are in a fairly advanced stage of preparation for publication. I'm hoping to have the validation study submitted to a journal within the next month or so. One of my colleagues Dr. St. Charles is working on a publication of the data from our large scale study of U.S. smokers.

Q: Does British American Tobacco have any plan to use this analysis in the future?

A: Yes. This year we started to use this technique and we are hoping to complete eight BAT Group markets this year. We are underway in Australia and New Zealand at the moment.

Q: And do you have any intention to bring this methodology and the results of your studies to the W.H.O.'s working group that you told us about earlier?

A: Of course. This data is directly relevant to the remit of that working group.

Q: Doctor, when the nicotine in the smoke of a cigarette exits the cigarette, is it in the gas form or the particulate form or both?

A: It is virtually entirely in the particulate form. Regardless of whether the nicotine is free or bound, as it exits the cigarette practically all of the nicotine, free and bound, will be in the particulate phase.

Q: What are you relying upon for that opinion?

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A: I am relying upon a number of things. There were some early studies done by the tobacco companies which were published in the 1980s looking at the partitioning of the nicotine. Those I reviewed in the publication in 2000, Dixon Seeman and Lambing (JD-010350) And then more recently, I am relying on a piece of work that was commissioned by the U.K. Department of Health from the Laboratory of the Government Chemist in the U.K., which talked about this very issue; whether nicotine is associated with the particulate phase or the gas phase. And it concluded that nicotine is quite clearly almost entirely, about 99.9%, in the particulate phase.

Q: During the act of smoking, does free nicotine evaporate from the particulate phase into the gas phase?

A: Yes, it does so during the inhalation phase of smoking.

Q: What causes the free nicotine to evaporate?

A: The main cause of evaporation is a dilution effect. When the smoke is drawn into the mouth, it is quite concentrated. If you then dilute it by going from 40 or 50 milliliters to 500 milliliters or a liter, you have increased the volume of the smoke by more than a magnitude, causing evaporation to occur.

Q: What happens to the nicotine that is not free?

A: It seeks equilibrium. As free nicotine evaporates from the particle, then more free nicotine is formed from the existing bound nicotine to maintain a proportion of free to bound nicotine, in other words, to maintain equilibrium. As more evaporates, more is formed. This continues until eventually we find virtually all of it will evaporate.

Q: What is process called?

A: Partitioning.

Q: And how rapidly does this occur?

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A: Very rapidly.

Q: Milliseconds?

A: Yes.

Q: Now, when did BATCo first begin researching this partitioning effect?

A: BATCo started researching that in the mid 1960s.

Q: And why were they doing that research?

A: Because they were investigating the impact sensation. At the time there was a well established relationship between the amount of nicotine in smoke and the intensity of the impact sensation. But it was also observed that two products that had the same amount of nicotine, could have different levels of impact. It appeared that this was due to different blend styles. Burley tobaccos that were slightly more alkaline than flue-cured were associated with a higher degree of impact. It was also known that more alkaline tobaccos were associated with more free nicotine, so it was thought that the impact sensation may be governed more so by the free nicotine content of smoke rather than the total nicotine. They were trying to understand the relationship between the chemistry of smoke and the sensory response of impact.

Q: At the time that BATCo was doing this work, was it known in the scientific community that nicotine could be found in either the free or bound form?

A: Yes, that's been known for several decades.

Q: What did BATCo do to research the relationship between free nicotine and impact?

A: One of the problems initially was measuring free nicotine. There wasn't an assay or test that could be used to quantify the amount of free nicotine that was present.

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To solve this problem BATCo developed a system that would produce what they called extractable nicotine.

Q: What is extractable nicotine? Is there a definition of that?

A: Not really a definition. I could give you the definitions that apply to the BATCo experiment. Basically what they did was collect the smoke condensate and suspend it in water. To this they added chloroform which forms an organic layer that floats on top of the water much like oil would. During the experiment free nicotine extracted out of the solution and migrated into the chloroform. And as it did bound nicotine formed free nicotine to maintain equilibrium. If the experiment continued long enough, all of the nicotine would extract into the chloroform. Of course, the experimental conditions were standardized so that the experimental conditions that effected the amount of extractable nicotine, such as the length of time of the experiment, were the same for each experiment. So really, the definition of the term extractable nicotine, as used by BATCo, was the amount of nicotine extracted from an aqueous solution into a layer of organic solvent, chloroform, under specific experimental conditions.

Q: How did the extractable nicotine produced in these experiments relate to the free nicotine that would be in the smoke from the same tobacco blend cigarette?

A: First of all, you could not state that if you had eighteen percent extractable nicotine in the experiment, that meant there was eighteen percent of free nicotine in the mainstream tobacco smoke. It couldn't tell you that. It wasn't a direct one-to-one relationship. The partitioning of nicotine in smoke is dictated by an entirely different set of conditions than the extraction of nicotine from an aqueous solution into chloroform. The extractable experiments would help to identify the factors that would affect free nicotine in smoke because a factor that affected the amount of extractable nicotine would most probably affect the conversion of bound nicotine to free in smoke. However, it was not possible to extrapolate the absolute magnitude of an effect of a factor from one experimental condition to the other.

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Q: Was pH a factor that affected the production of free nicotine and extractable nicotine?

A: Yes. If you took the condensate, suspended it in water, measured the pH, which is scientifically valid as you have created a dilute aqueous solution, a condensate producing a higher pH would be associated with a higher amount of extractable nicotine. While BATCo could not measure the pH in smoke, they understood that smoke would react in a similar way, so the extractable nicotine experiments provided a useful test system giving an indication of directional changes, i.e., an increase or decrease in extractable nicotine was likely to be associated with an increase or decrease in the amount of free nicotine in the smoke.

Q: Does that mean that the pH of a tobacco condensate in the aqueous solution is the same as the pH of the smoke from the same tobacco?

A: No, it's completely different. pH by definition is a measure of hydrogen ion concentration in an aqueous solution at equilibrium. So inserting a pH probe into the aqueous solution in the experimental setup will give a scientifically valid measure of the pH of the solution. However, with regard to a smoke particle, it's neither a dilute aqueous solution nor is it at equilibrium. Therefore, in strict scientific terms, the concept of pH doesn't really apply to the smoke particle. However, it is valid to extrapolate directional changes in pH in what I'd term a dilute aqueous solution of smoke condensate to what may happen in the smoke particle. If, for example, a blend change or an ingredient added to tobacco increased the pH of the aqueous extract of smoke condensate, then it is likely that an increase in the amount of bases in the smoke particle would also occur through such a blend or ingredient intervention. Similarly, if a blend or ingredient intervention produced no effects on the pH of an aqueous extract of smoke condensate, then one can reasonably predict that it would not change the acid-base balance of the smoke particles. Indeed, this issue was discussed in some detail in the Dixon, Seeman and Lambing 2000 publication. (JD-010350).

Q: Have various means of measuring smoke pH been proposed?

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A: Yes, there are a number of ways people have tried to do this. But they all suffer from the basic problem that cigarette smoke is not a dilute aqueous solution at equilibrium.

Q: Were there experiments performed at BATCo with respect to the addition of ammonia?

A: Yes. In reviewing historic BATCo studies I discovered that there was work done in early years, around 1963 to 1965 by Sam Evelyn. These experiments involved the addition of high levels of ammonia gas to tobacco in an attempt to make safer cigarettes by reducing the levels of aldehydes in smoke. A number of aldehydes such as formaldehyde were known to be respiratory irritants. And it was thought to be a good idea to reduce the levels of formaldehyde and other related aldehydes. The experiments conducted by Sam Evelyn involved passing gaseous ammonia through the tobacco for up to 16 hours followed by an 'air wash' for a further 36 hours. The treated tobacco was used to make cigarettes and the smoke from these experimental cigarettes was chemically analyzed.

Q: What was the result?

A: Whilst ammonia did reduce the level of aldehydes it had some undesirable effects on the tobacco. It blackened and fermented the tobacco and completely changed the sensory characteristics of the smoke in a negative way.

Q: Did BATCo examine the use of ammonia again?

A: Yes. In the 1980s Brown and Williamson reversed engineered Marlboro and concluded that the use of ammoniated tobacco sheet in the manufacture of Marlboro cigarettes was an important component of Marlboro's success in the market. Brown and Williamson believed that ammonia improved the sensory aspects and gave Marlboro what Brown and Williamson regarded as its superior Burley character.

Q: Are you familiar with the Leaf Blender's Manual, which is US 86,908?

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A: Yes. This was a manual produced by researchers at Brown and Williamson and it addressed the use of ammonia compounds in the manufacture of reconstituted tobacco.

Q: Did the Leaf Blender's Manual set forth the smoke qualities that Brown and Williamson thought ammonia improved?

A: Yes, if you look at that the manual, you see there is a whole list of sensory properties which they attribute at least in part to the use of ammonia compounds.

Q: Did the Leaf Blender's Manual also suggest that there was an increase in the amount of nicotine transferred from the tobacco into the smoke?

A: Yes, they certainly did. Relying upon the data in JDEM-030023 the researchers concluded that there was an increase in nicotine transfer as the result of using ammoniated sheet. However the researchers misinterpreted the data.

Q: Before we get to the misinterpretation, please explain JDEM-030023.

Leaf Blender's Manual

TABLE 2

SMOKE ANALYSIS OF CIGARETTES CONTAINING VARYING LEVELS OF CPCL AND EBR

Percent in Blend CPCL	Percent in Blend EBR	Tar (mg)	Nicotine (mg/cig)	Puffs	Nicotine Transfer	Tar/Nic. Ratio
0	11	14.7	1.14	8.7	[illegible]	[illegible]
4	11	16.3	1.20	8.8	[illegible]	[illegible]
8	9	16.3	1.26	8.8	15.87%	12.9
12	5	16.4	1.28	9.0	17.84%	13.0
17	0	16.7	1.29	9.2	18.16%	12.9

Source: US Ex. 86908 JDEM-030023

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A: This table reports the data from a study that compared the smoke deliveries of experimental cigarettes containing different levels of two reconstituted sheet tobaccos. The first reconstituted sheet, CPCL, was made with ammonia. The second, EBR, was made without ammonia. So the top row on the table, the one highlighted in pink, contains the data on delivery from an experimental cigarette with EBR sheet made with no ammonia and the bottom row, highlighted in yellow, is the data from cigarettes with 17% CPCL -- the ammoniated sheet.

Q: How was the data misinterpreted?

A: If you compare the smoke nicotine from the ammoniated CPCL cigarette with that from the nonammoniated it was higher, 1.29 to 1.14, but the difference was not because of an increased transfer of nicotine to smoke. Rather, the increased nicotine was due to the extra puff resulting from the slower burning ammoniated CPCL cigarette. This can be clearly shown by the increase in puff number, 9.2 versus 8.7, and by the increase in tar from the CPCL cigarette with ammonia, 16.7 versus 14.7. Finally, if nicotine transfer to smoke was actually increased, one would expect to see a bigger increase in the nicotine delivery than you would in the tar delivery. That would be reflected in a change of the tar to nicotine ratio. When you look at the tar to nicotine ratio, you can see from the table that they are identical, 12.9 versus 12.9. With or without ammoniated recon, it gives you the exact same tar to nicotine ratio. That means that the nicotine transferred from the tobacco to the smoke was not increased by the use of ammonia.

Q: Was this mistake pointed out to B&W?

A: It was. Very shortly after the manual was circulated.

Q: Have you subsequently dealt with the issue of ammonia in greater detail Dr. Dixon?

A: Yes I have.

Q: And how did that come about?

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A: It really came about in 1999 when the group called Action on Smoking and Health or ASH, in the U.K., published an article on their website about cigarette ingredients. They made an allegation that the tobacco companies were using ammonia in their products in order to increase things like nicotine transfer, to increase the rate in which nicotine is absorbed from smoke and the rate in which nicotine gets to the brain of smokers. It wasn't a peer reviewed publication. It was simply an article posted on their website. The U.K. Department of Health picked up the article and were naturally concerned about it. They contacted the U.K. Tobacco Manufacturers Association and asked for a response from the industry.

Q: What did the manufacturers association do?

A: First of all, they wrote back to our Department of Health and told them that we did not believe that the ASH article was a scientifically valid evaluation of the use of tobacco ingredients. The Department of Health then asked for more detail. As a result, I and two other industry scientists, put together a presentation which I delivered to senior members of the U.K. Department of Health and their scientific advisors. At the end of the meeting, I put together a fairly lengthy document summarizing all of the papers and information we presented and gave that to the Department of Health.

Q: After your Department of Health presentations and the submission of the paper, did you do anything further with your work on reviewing the ammonia issue?

A: Yes. My colleagues and I prepared a review on the issue which was published in the year 2000.

Q: What were the conclusions of the paper?

A: There were a number of conclusions about ammonia. We concluded from our review of the scientific data that ammonia compounds used in the manufacture of commercial cigarettes:

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- Serve as processing agents in the manufacture of certain types of reconstituted tobacco sheet.
- Contribute to the flavour properties of cigarette smoke from US blended styles of cigarettes.
- Do not increase the amount, rate or efficiency of nicotine transferred from tobacco to mainstream smoke.
- Do not increase the nicotine content of mainstream cigarette smoke.
- Have no influence on the determination of mainstream nicotine yield when the FTC/ISO method is used (and the FTC/ISO method captures >99% of mainstream nicotine).
- Do not increase the amount or total rate of nicotine absorbed by the smoker.
- Do not increase the total amount and rate of nicotine uptake to the central nervous system.
- May increase the amount of nicotine absorbed in the mouth and upper respiratory tract.
- May decrease the total amount and overall rate of nicotine absorption and flow to the central nervous system.
- Do not appear to increase the "pH of smoke" under commercial use levels.

Q: Did you do further research on this?

A: We recognized there was one area which would benefit from a direct experiment in which we would measure the effect of the addition of commercial levels of ammonium compounds to tobacco by measuring both the rate and the amount of nicotine deposited in the respiratory tract and the rate and amount of nicotine absorption in the blood of smokers of either untreated control cigarettes or identical cigarettes containing added ammonium compounds.

Q: Before we get to that, are you familiar with a paper by Dr. Henningfield published in 2004 that addressed the need for direct experimental research on ammonia?

A: Yes.

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Q: Could you explain the type of experiment that Dr. Henningfield said was needed?

A: Yes. In the paper he stated that control studies should be conducted using cigarettes with and without ammonia treatment to see how the use of ammonia or ammonia precursors influences the uptake of nicotine.

Q: When he was writing this and publishing this paper, where were you in terms of your experiment on ammonia?

A: We had finished our experiment on ammonia. I analyzed all the data and produced a publication and we then submitted it to Chemical Research and Toxicology and it was published in 2004 after Dr. Henningfield's paper.

Q: In your opinion, how did your experiment relate to the experiment called for by Dr. Henningfield?

A: I would say that our experiment was the exact duplicate of the type of study that Dr. Henningfield and his co-authors found was needed to provide definitive answers to the questions that had been raised about ammonia.

Q: What were the findings of your experiment?

A: First of all, we confirmed some of the observation that we had made in our review. For example, the use of commercial levels of ammonia, or diammonium phosphate, did not elevate the smoke pH as measured by our aqueous extract method. We confirmed that. And we also compared the nicotine yields and the tar yields, puff numbers, et cetera, and we confirmed there was no difference in the nicotine/tar ratio with or without the use of ammonia. This confirmed that there wasn't an elevated nicotine transfer from tobacco to smoke resulting from the use of ammonium compounds.

Q: And what about the issue of the rate of nicotine delivery to the brain by use of ammonia?

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A: We confirmed that there was no evidence from our experiment that ammonia enhanced delivery to the brain. We found that the amount of nicotine absorbed into the lung was the same with or without the addition of ammonia generating compounds. And by looking at blood levels of nicotine, during and after people were smoking a cigarette, we found there was no increase in either the amount or the rate of nicotine being absorbed from the lung. So our conclusions were, in terms of chemistry and in terms of human physiology and pharmacology, that the ammonia made no difference at all to the nicotine uptake in smokers.

Q: Or the speed?

A: Or the speed. If ammonia did effect the rate of absorption of nicotine, the blood level of nicotine measured during and after smoking should have reached a higher peak, and reached it sooner, in those smoking cigarettes with ammonia added than those smoking cigarettes with no ammonia. They did not. The addition of ammonia during the commercial manufacture of cigarettes does not increase the speed of the absorption of nicotine.

Q: Doctor, if ammonia did increase the pH, and more free nicotine was liberated into the gaseous form upon inhalation, what would happen?

A: The site of absorption would change.

Q: How?

A: If you increased the amount of free nicotine in smoke you would alter the site of absorption in favor of more absorption in the upper airways and less in the lower airways.

Q: What would the result be in terms of speed to the brain?

A: Increasing the amount of free nicotine would result in a slower rate to the brain.

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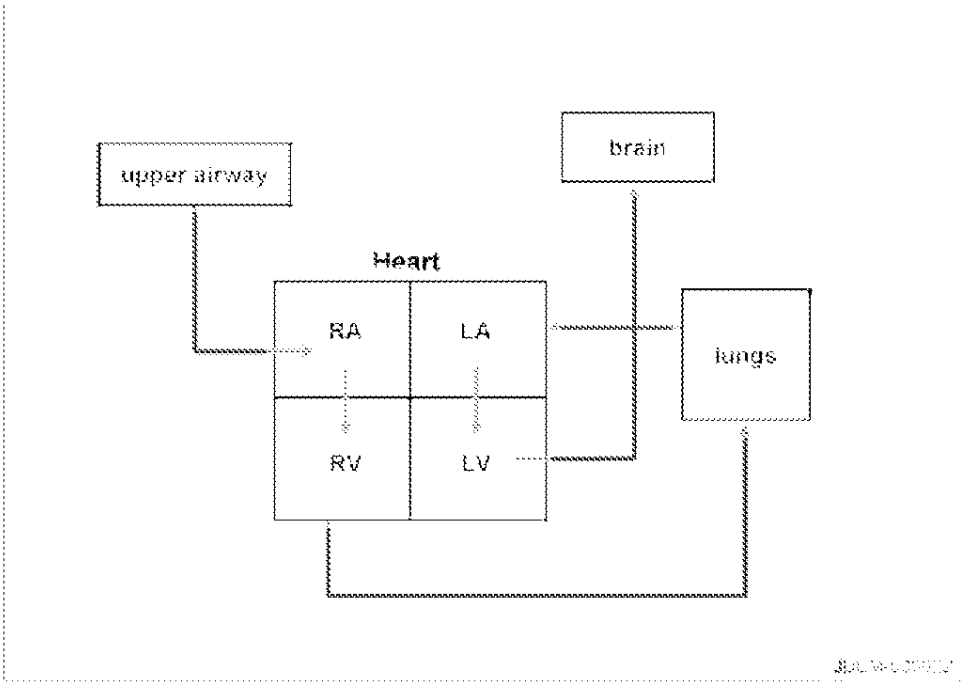

Q: Does JDEM-030022 help explain why?

A: Yes. If the nicotine is absorbed in the throat, it has a very torturous route to the brain. First of all, the blood supply is much smaller compared to the lung. So the nicotine would get into a much weaker blood supply, and once it gets into the blood supply, it would go into what is called the venous return. This means that the nicotine would travel down back to the right heart, then travel through the right heart into the pulmonary circulation and then eventually return to the left side of the heart. The nicotine would then enter the arterial circulation some of which would enter the CNS. In contrast, if the nicotine is absorbed in the alveolar region of the lung, you bypass that venous return. Following alveolar absorption nicotine is taken into the capillaries of the lung, passed from the lung directly to the left heart and then straight into the arterial circulation. Hence absorption from the alveolar region provides a much faster route to the brain than absorption from the upper airways.

Q: The major selling brand during your time at BATCo was what?

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A: A brand called State Express 555.

Q: And what brand style of BATCo cigarettes was sold in the United States?

A: State Express 555, a flue-cured product.

Q: And did that cigarette ever use ammonia?

A: No.

Q: Why not?

A: Because, as I mentioned earlier on, the main use of ammonia technology is to enhance the flavour character of Burley tobacco. It improves the Burley character. State Express 555 doesn't use Burley tobacco. It's a predominantly flue-cured product with a small amount of Oriental tobacco. Ammonia technology would not result in any sensory improvement of such a product, hence the reason why ammonia technology was not used on this brand.

Q: Were there other topics that you presented on to the U.K. Department of Health in 1999?

A: Yes. We presented on the issue of acetaldehyde.

Q: Why was the Department of Health interested in acetaldehyde?

A: Again, the DOH looked at the ingredients paper on the ASH website and it contained an allegation that sugars were added to tobacco in order to form acetaldehyde because it acted synergistically with nicotine to enhance central nervous system effects of nicotine.

Q: Are sugars added to tobacco of all cigarettes?

A: No, primarily they are added to products that use Burley tobacco, products such as U.S. blended cigarettes. However, they tend not to be added to flue-cured tobacco cigarettes like our State Express 555s.

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Q: What was the source for the hypothesis that acetaldehyde in conjunction with nicotine produced an enhanced effect on the body?

A: The source for that was some work that was conducted by Dr. Victor DeNoble when he was a researcher for the Philip Morris company in the 1980s. DeNoble did some experiments with rats in which he trained rats to self-administer nicotine under experimental conditions. Then he looked at what happened when he combined nicotine with acetaldehyde. According to his experiments, he determined that it increased the rate of self-administration of nicotine. DeNoble interpreted that to mean that acetaldehyde was potentiating the effect of nicotine in the brain.

Q: Did you review that work?

A: I did. I have a copy of DeNoble's research reports from the mid 1980s. He was looking at a very small number of rats in his acetaldehyde and nicotine synergy studies. And the data were not consistent. The study was not, as far as I am aware, ever repeated or published. I have certainly never seen anything that confirms the results that DeNoble produced in the early 1980s.

Q: When was Dr. DeNoble's work first publicized outside of Philip Morris?

A: I believe it was around 1994 or 1995 when DeNoble raised this. It was in either a deposition for trial or maybe even in testifying for a trial.

Q: Dr. Wigand testified that Brown and Williamson was working on the issue of the enhanced effects of acetaldehyde and nicotine at the time he was there and before. Are you aware of any work that B&W or BATCo did on the synergistic effects of acetaldehyde and nicotine?

A: No, not at all.

Q: Do you know of any research by B&W that suggested that nicotine and acetaldehyde could react synergistically to enhance pharmacological effects?

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A: No, I am not aware of any suggestion like that.

Q: Have you researched this issue of whether acetaldehyde and nicotine could act synergistically to enhance pharmacological effects?

A: Yes, I have. The Department of Health had asked us to brief them on that issue as well so we produced a presentation on acetaldehyde for the Department of Health.

Q: Did you subsequently publish that presentation?

A: We did more than that. We produced a full scientific review of the whole area of acetaldehyde chemistry and pharmacokinetics.

Q: Was that published?

A: Yes, in Chemical Research in Toxicology in 2002. (JD-031677; JDEM-030026)

Q: How did it happen that your article was on the cover of the issue?

A: Each time Chemical Research in Toxicology publishes an edition of their journal, they look at the papers that are going into that edition. The Board selects the one that they believe is the best article. We were delighted that it was published, but we were even more honored to have it as the cover page.

Q: What did your study show with respect to acetaldehyde?

A: It confirmed that acetaldehyde in smoke is not produced by sugars that are added to tobacco. Acetaldehyde is produced by the combustion of cellulose that is naturally present in tobacco.

Q: Did BATCo research what would happen to aldehydes such as acetaldehyde if sugar was added?

A: Yes. We found that the addition of sugars didn't increase acetaldehyde levels in cigarette smoke and in fact Thornton and Massey published those findings in 1975.

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Q: Was that research available to Dr. Wigand when he was at Brown and Williamson?

A: Yes, of course. It was available to anyone. It was a publication.

Q: What else did your study conclude about acetaldehyde?

A: We knew that if acetaldehyde is present in the brain, it does have pharmacological properties. What we found from our review is that the main source of acetaldehyde in the brain is from alcohol. So if a person drinks alcohol, the alcohol travels to the brain crosses the blood brain barrier and enzymes break down the alcohol in the brain and one of the compounds it produces is acetaldehyde. The next thing we looked at was whether the studies show that if you were to deliver acetaldehyde at the levels present in cigarette smoke, would there be sufficient acetaldehyde there to cross the blood brain barrier and initiate pharmacological effects in the brain. Our review identified a number of papers which show that this isn't the case. Firstly, there are enzymes in the lung and blood, and at the blood brain barrier which break down acetaldehyde before it can cross the blood brain barrier. This means an extremely high level of acetaldehyde would need to be inhaled in order for it to overcome this very effective enzyme system. Secondly, a number of researchers have studied the effects of smoking cigarettes on acetaldehyde levels in the blood and these unanimously show that cigarette smoking does not increase the natural levels of acetaldehyde in the blood. So we concluded that acetaldehyde from cigarette smoke does not increase acetaldehyde delivery to the brain.

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